STUDIES ON HETEROCYCLIC COMPOUNDS OF THERAPEUTIC IMPORTANCE

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IN
THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE
OF

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The work included in the thesis is my own work under the supervision of ***Dr. N. A. Chauhan*** and leads to some contribution in chemistry subsidised by a number of references.

Dt. : .03.2006 ***(Ronak K. Patel)***
Place : Rajkot.

This is to certify that the present work submitted for the Ph. D. Degree of Saurashtra University by ***Ronak K. Patel*** is his own work and leads to advancement in the knowledge of chemistry. The thesis has been prepared under my supervision.

Date : -03-2006
Place : Rajkot.

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Dedicated to
My Parents

ACKNOWLEDGEMENTS

Hats off to the Omnipresent, Omniscient and Almighty God, the glorious fountain and continuous source of inspirations! I offer salutations to him and my head bows with rapturous dedication from within my heart, to the Omnipotent Lord "Shri Krishna".

"No man is perfect", the mistakes are mine the touch of perfection is His. "A helping hand" never expects thanking notes nor asks for acknowledgement. But I want to thank my respected guide Dr. N. A. Chauhan, Rtd. Professor, Department of Chemistry, Saurashtra University, Rajkot, for his kindness, his ever attentive and listening ear in our hour of need and for his striving to make us not only better in our chosen field but good human being. I pray to God that I may come to his expectations in present as well as in future.

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Nobody is able to give justice in giving entirely and adequately thanks to parents for giving gift of life and nurturing it. My vocabulary fails to express my feelings and acknowldging the tremendous debt to my esteemed father Dr. K. R. Patel & my loving mother Savitaben.

Also, I can never forget my beloved brother, Saumit, whose continuos flow of love helped me to reach the goal.From bottom of my heart, I thank my wife, Snehal, whose support and constant inspiration made me to complete my work succcessfully.

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I also remember well wishers and all those persons who helped me directly or indirectly for preparation of this work.

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Finally, I express my greatful acknowledgment to the authorites of Saurashtra University for providing me research facilities.

RONAK K. PATEL

CONTENTS

SYNOPSIS

The research work incorporated in the thesis with the title **"STUDIES ON HETEROCYCLIC COMPOUNDS OF THERAPEUTIC IMPORTANCE"** has been described as under.

[A] STUDIES ON CHALCONES

[B] STUDIES ON PYRAZOLES

[A] STUDIES ON CHALCONES

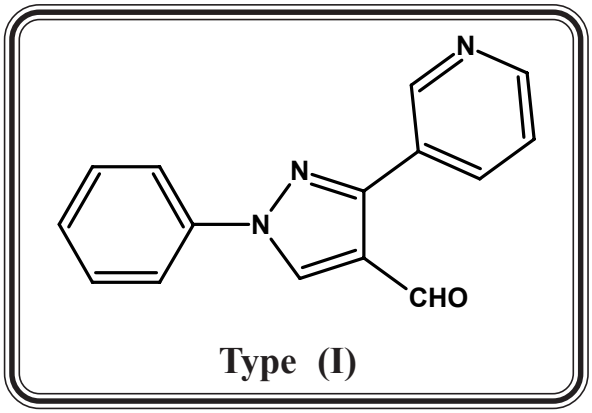
The chalcones containing an active keto-ethylenic linkage are well known intermediates in the synthesis of heterocyclic compounds. They are exhibiting various biological activities such as antibacterial, analgesic, anthelmintic, antiinflammatory, antitubercular, antifungal, antimicrobial etc.

The chalcones are good intermediate for the preparation of numerous heterocyclic compounds like pyrazolines, oxopyrimidine, thiopyrimidine, cyanopyran barbitones, aminopyrimidine, cyanopyridine, and thiosemicarbazones which have been described as following parts.

PART-I : STUDIES ON PYRAZOLINE DERIVATIVES

Pyrazolines have played important role in medicinal chemistry. We have synthesise pyrazoline as under.

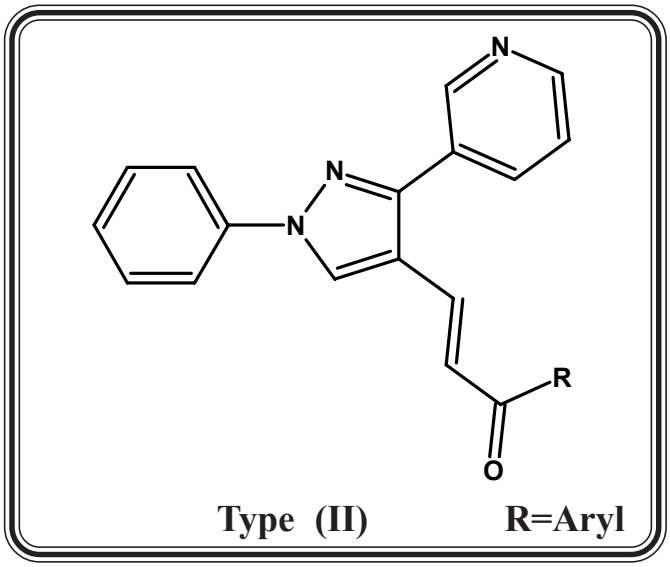
SECTION–I : Preparation and biological evaluation of 1,N-Phenyl-3-β-pyridyl-4-formyl pyrazole



Type (I)

Pyrazole aldehyde of type (I) was prepared by the action of DMF and $POCl_3$ on phenylhydrazone of 3-acetyl pyridine.

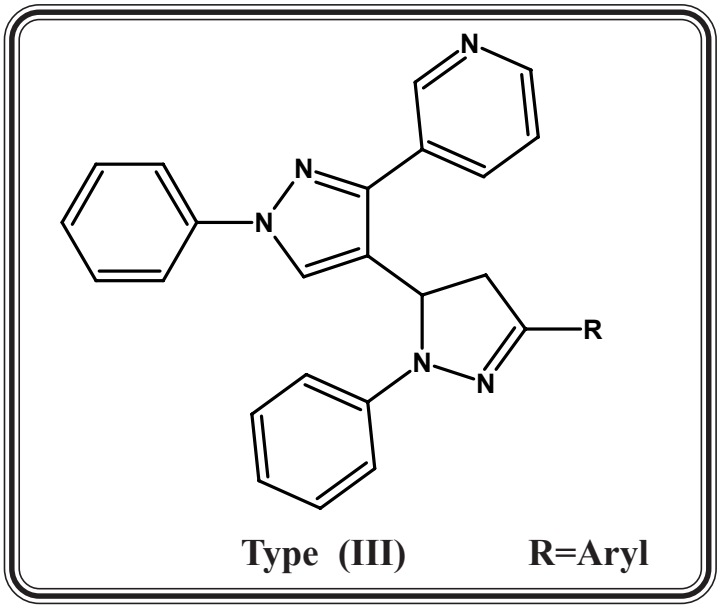
SECTION–II : Synthesis and biological evaluation of 1-Aryl-3-(1',N-phenyl–3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-ones



Type (II) R=Aryl

The chalcone derivatives of type (II) have been prepared by the condensation of 1,N-phenyl-3-β-pyridyl-4-formyl pyrazole with different aryl ketones in presence of 40% NaOH.

SECTION–III : Synthesis and biological evaluation of 1,N-Phenyl-3-aryl-5 (1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-pyrazolines



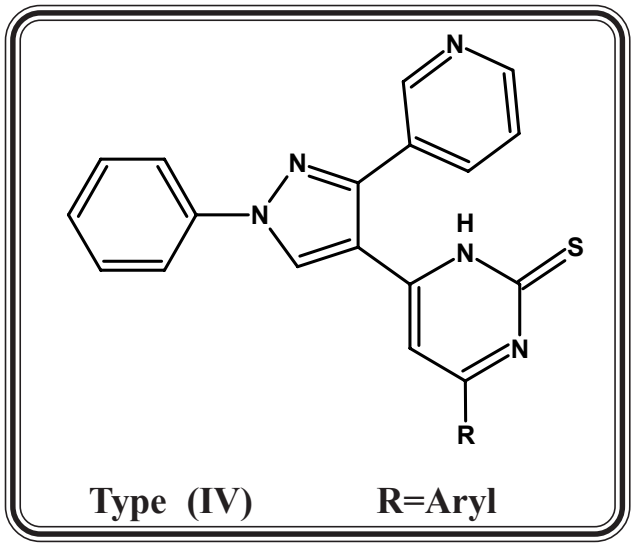
Type (III) R=Aryl

The pyrazoline derivatives of type (III) have been prepared by the reaction of type (II) with phenyl hydrazine in presence of basic catalyst like piperidine.

PART-II : STUDIES ON PYRIMIDINES

Pyrimidine derivatives have been reported to possess various biological activities like antitubercular, antifungal, herbicidal, diuretic etc. Led by these considerations, it was contemplated to synthesise some pyrimidine derivatives which have been described as under.

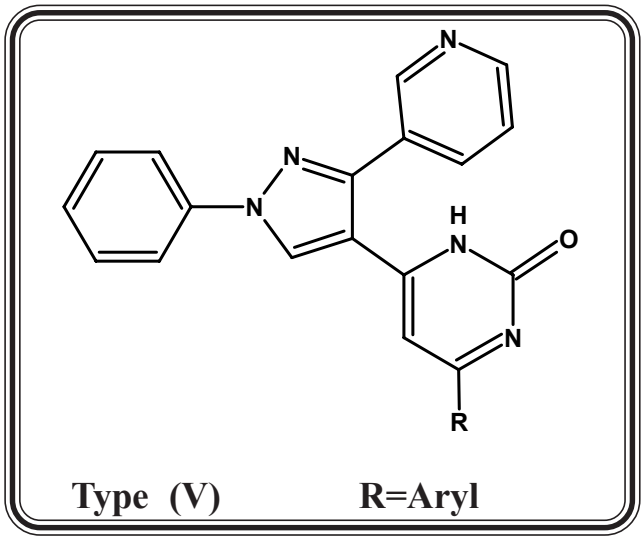
SECTION–I : Synthesis and biological evaluation of 6-Aryl-4-(1',N-phenyl-3'-β-pyridyl-1H-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-thiones



Type (IV) R=Aryl

Thiopyrimidines of type (IV) have been synthesized by the condensation of chalcones of type (II) with thiourea in presence of alcoholic KOH.

SECTION–II : Synthesis and biological evaluation of 6-Aryl-4-(1',N-phenyl-3'-β-pyridyl-1H-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-ones



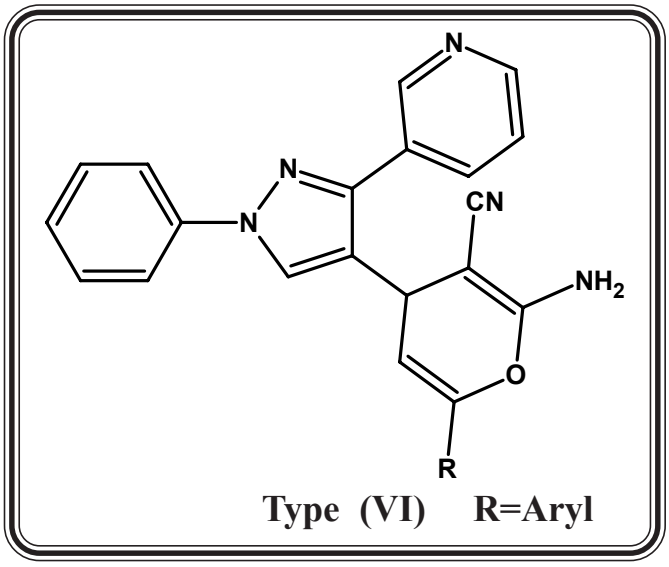
Type (V) R=Aryl

Pyrimidinones of type (V) have been synthesized by the condensation of chalcones of type(II) with urea in presence of alcoholic KOH.

PART-III : STUDIES ON CYANOPYRANS

Cyanopyran derivatives have been reported to possess various pharmacological activities such as antibacterial, antifilarial, antifungal, anticoagulant etc. Keeping this in view to achieve better potency different types of cyanopyran derivatives have been described as under.

SECTION–I : Synthesis and biological evaluation of 2-Amino-6-Aryl-3-cyano-4-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-4H-pyrans



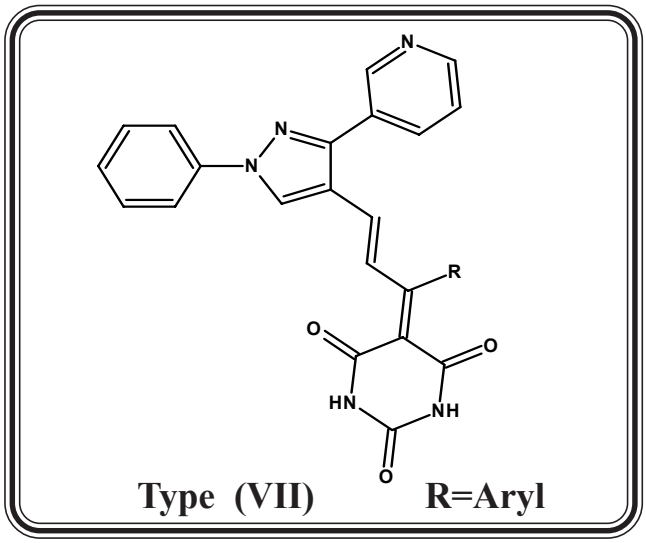
Type (VI) R=Aryl

Cyanopyrans of type (VI) have been synthesized by the condensation of chalcones of type (II) with malononitrile in pyridine.

PART-IV : STUDIES ON BARBITONES

Barbitones plays a vital role owing to their wide range of biological activities like antitumor, antiinflammatory, antitubercular and antidiabetic etc. Synthesis of some novel barbitone derivatives have been undertaken in order to assess their pharmacological profile, which have been described under.

SECTION–I : Synthesis and biological evaluation of 5-[1-Aryl-3-(1',N-phenyl-3'-β-pyridyl-1H-pyrazol-4'-yl)-prop-2-enylidene]pyrimidine-2,4,6 (1H,3H,5H)-triones



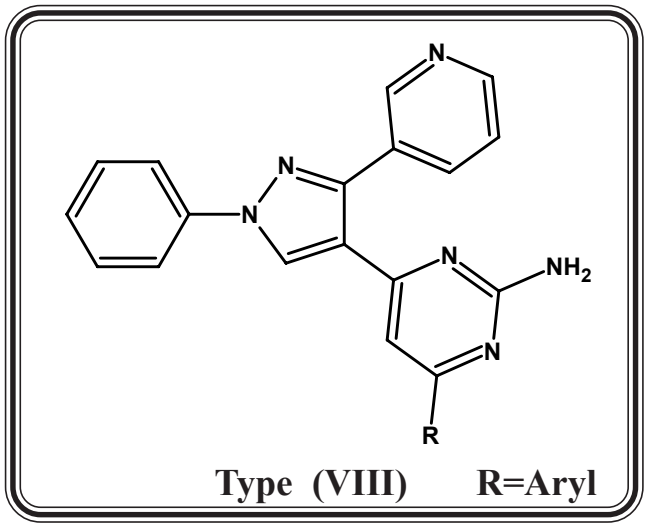
Type (VII) R=Aryl

Barbitone derivatives of type (VII) have been prepared by the condensation of type(II) with barbituric acid.

PART-V : STUDIES ON AMINOPYRIMIDINES

It has been reported that pyrimidine derivatives are associated with various biological activities like antifungal, antitubercular, antibacterial, herbicidal etc. These valid observations led us to synthesise aminopyrimidine derivatives which have been described as under.

SECTION–I : Synthesis and biological evaluation of 2-Amino-4-aryl-6-(1',N-phenyl-3'-β-pyridyl-1H-pyrazol-4'-yl)pyrimidines



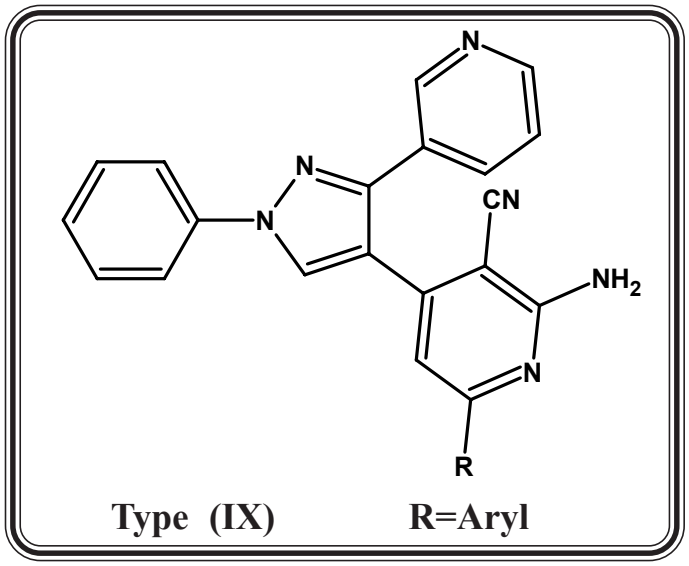
Type (VIII) R=Aryl

The compounds of type (VIII) have been synthesized by the condensation of type (II) with guanidine hydrochloride in basic media.

PART-VI : STUDIES ON CYANOPYRIDINES

Cyanopyridine plays a vital role owing to their wide range of biological activities such as antihypertensive, antibacterial, antidiabetic and anticholestemic. They have been also used as dyes for cotton and polyester fabrics, it appeared of interest to design and synthesise cyanopyridine derivatives, which have been described as under.

SECTION–I : Synthesis and biological evaluation of 2-Amino-3-cyano-4-(1',N-phenyl-3'-β-pyridyl–pyrazol-4'-yl)-6-aryl-pyridines



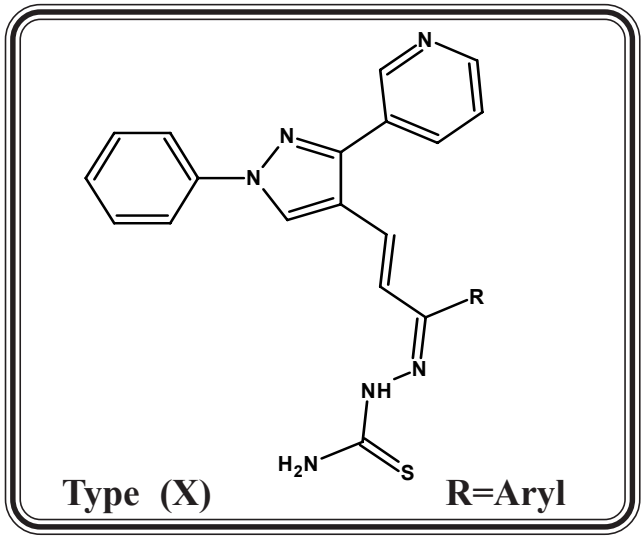
Type (IX) R=Aryl

2-Amino-3-cyanopyridines of type(IX) have been under taken by the condensation of chalcones of type(II) with ammonium acetate and malononitrile.

PART-VII : STUDIES ON THIOSEMICARBAZONES

The study of thiosemicarbazone as valuable drug for the diseases like tuberculosis, cancer, diabetes, malaria and leprosy is well known. In view of these facts, it was contemplated to synthesise thiosemicarbazone derivatives which have been described as under.

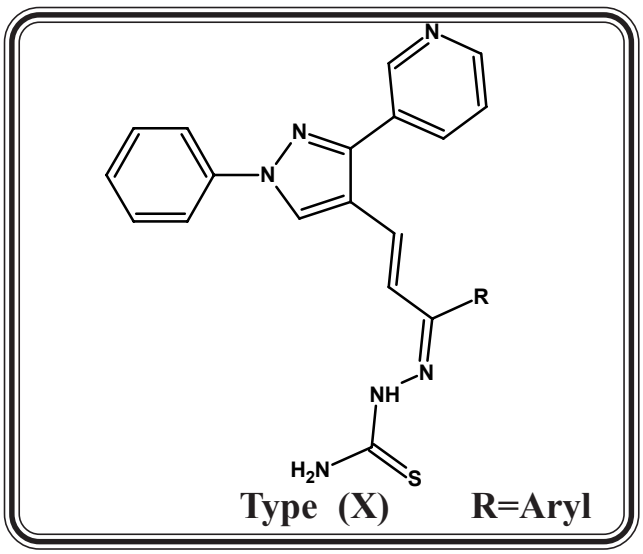
SECTION–I : Synthesis and biological evaluation of 1-Aryl-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propene-1-thiosemicarbazones



The thiosemicarbazones of type(X) have been prepared by the condensation of chalcones of type (II) with thiosemicabazide.

SECTION–II : Microwave induced an expenditous synthesis of 1-Aryl-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propene-1-thiosemicarbazones

In recent years, MORE (Microwave Induced Organic Reaction Enhancement) technique has become very popular due to substantial reduction in reaction time, operational simplicity and formation of cleaner reaction products. Keeping these facts in view, we have synthesised thiosemicarbazone derivatives using microwave irradiation.



The thiosemicarbazones of type(X) have been prepared using microwave irradiation of chalcones of type (II) with thiosemicabazide.

[B] STUDIES ON PYRAZOLES

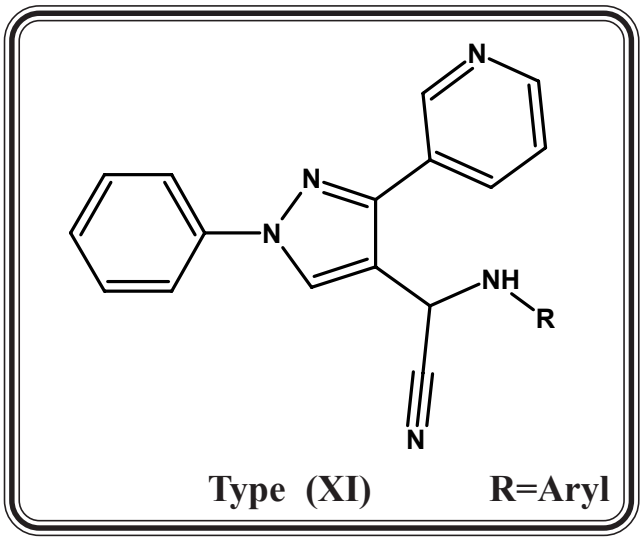
Pyrazole derivatives are associated with broad spectrum of pharmacological activities like antitubercular, antimicrobial, hypnotics, antiinflammatory, antitumor, plant growth regulators and are also used as herbicidal and insecticidal.

Looking to the diversified biological activities, it appeared of interest to synthesise some acetonitrile, azomethine and thiazolidinone.

PART-VIII : STUDIES ON α-ARYLAMINONITRILES

Nitriles have been reported to be active as antibacterial, antifungal, antipyretic and antimalarial etc. In order to achieve better biological activity, we have synthesised some new nitrile derivatives bearing pyrazoline nucleus, which is described as under.

SECTION–I : Preparation and biological evaluation of α-Arylamino-1,N-phenyl-3-β-pyridyl-pyrazol-4-yl-acetonitriles



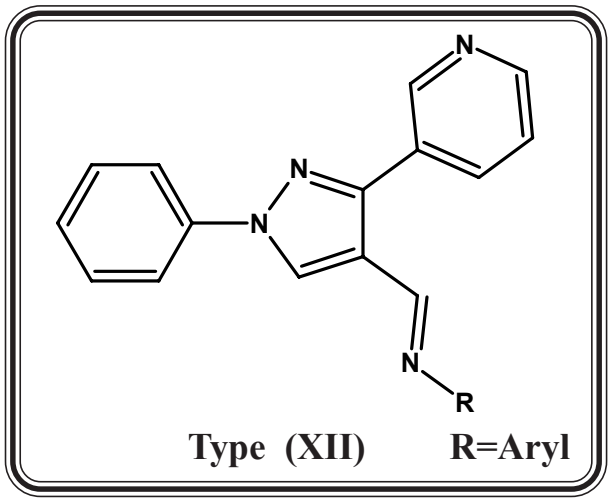
Type (XI) R=Aryl

Nitriles of type(XI) have been synthesized by the condensation of different aromatic amines with type(I) by using potassium cyanide in presence of glacial acetic acid at 0-5^{o}C.

PART-IX : STUDIES ON N-ARYL-1,N-PHENYL-3-β-PYRIDYL-4-YL-AZOMETHINES

Azomethine derivatives represent one of the modest classes of compounds possessing wide range of therapeutic activities, such as antimicrobial, antimalarial, antibacterial. With a view to getting better therapeutic agents and to evaluate its pharmacological profile, different type of azomethine derivatives have been prepared, and reduction as under.

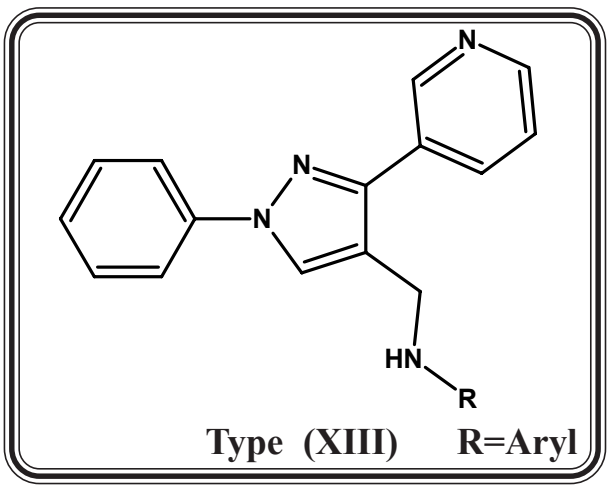
SECTION–I : Synthesis and biological evaluation of N-Aryl-1,N-phenyl-3-β-pyridyl-4-yl-azomethines



Type (XII) R=Aryl

The azomethines of type (XII) have been prepared by the condensation of type (I) with different aromatic amines.

SECTION–II : Synthesis and biological evaluation of 4-Arylaminomethyl -3-β-pyridyl-1,N-phenylpyrazoles



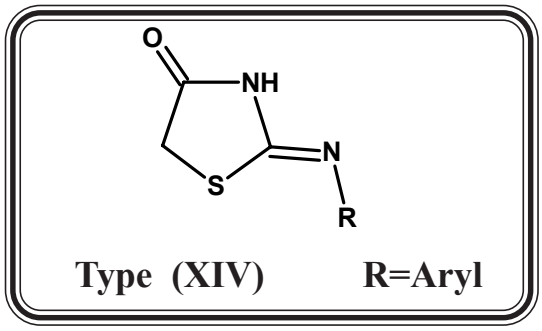
Type (XIII) R=Aryl

The compounds of type (XIII) have been prepared by the reaction of compounds of type (XII) with an. $NaBH_4$.

PART-X : STUDIES ON THIAZOLIDINONES

Compounds bearing thiazolidinone moiety are endowed with a variety of biological activities such as antimicrobial, CNS depressant, antitubercular, sedative, anticonvulsant etc. With a view to supplement these valid observations it was contemplated to synthesise some 4-thiazolidinone derivative which have been described in following sections.

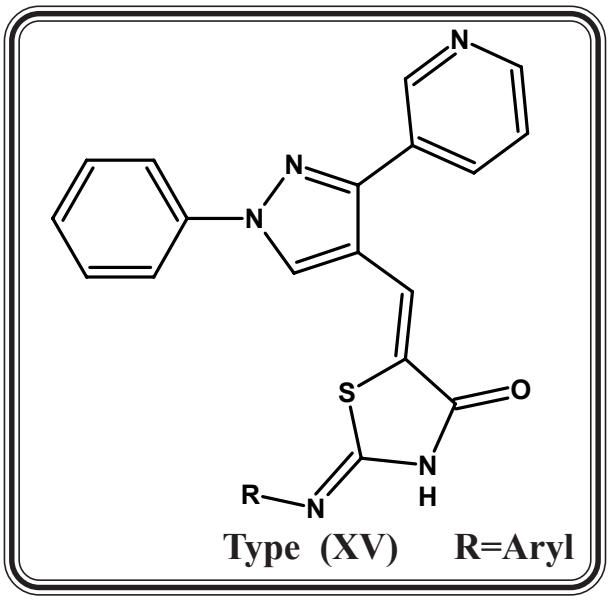
SECTION-I : Synthesis and biological evaluation of 2-Arylimino-5(H)-4-thiazolidinones



Type (XIV) R=Aryl

The thiazolidinones of type (XIV) have been prepared by the action monochloroacetic acid and sodium acetate in glacial acetic acid on thiourea derivatives of different aromatic amine.

SECTION-II : Synthesis and biological evaluation of 2-Arylimino-5-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl-methino)-4-thiazolidinones



Type (XV) R=Aryl

The thiazolidinones of type (XV) have been prepared by condensation of 1,N-phenyl-3-β-pyridyl-4-formyl pyrazole moiety with different type (XIV) in glacial acetic acid.

The constitution of newly synthesised compounds have been characterized using elemental analyses, Infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

***In Vitro* study on multiple biological activities:**

(1) All the compounds have been evaluated for their antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus Niger*** at a concentration of 40 ì g. The biological activity of the synthesized compounds has been compared with standard drugs.

(2) Selected compounds have been evaluated for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis $H_{37}R_V$*** at a concentration of 6.25 ì g/ml using Rifampin as standard drug, which have been tested at Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF), Alabama, U.S.A.

STUDIES ON HETEROCYCLIC COMPOUNDS OF THERAPEUTIC IMPORTANCE

INTRODUCTION

Heterocyclic chemistry has seen unparalled progress owing to their wide natural occurance, specific chemical reactivity and broad spectrum utility.

The variety of heterocyclic compounds is enormous, their chemistry is complex and synthesizing them requires great skill. Among large number of heterocycles found in nature, nitrogen hetero cycles are the most abundant than those containing oxygen or sulfur owing to their wide distribution in nucleic acid instance and involvement in almost every physiological process of plants and animals.

Most of the alkaloids which are nitrogenous bases occuring in plants and many antibiotics including penicillin and streptomycin have also heterocyclic ring system. Many natural pigments such as indigo, haemoglobin and anthocyanin are heterocycles. Most of the sugars are their derivatives including Vitamin C for intance, exist largely in the form of five membered. Vitamin B6 (Pyridoxine) is a derivative of pyrimidine essential in aminoacid metabolism.Important drugs, poisons and medicines (both natural and synthetic) such as sulphathiazole, pyrenthrin, rotenmone, strychnine, reserpine, certain of the antihistaminics, the ergot alkaloids caeffine, cocaine, barbiturates, etc. are heterocyclic compounds.

Heterocyclic compounds have great biological significance because :

1. They have a specific chemical reactivity.
2. They resemble essential metabolism and can also provide false synthons in biosynthetic process.
3. They fit receptors and block their normal working.
4. They provide convenient building blockers to which biologically active substituents can be attached.

The interesting biological activities of heterocycles have stimulated considerable research work in recent years including to the synthetic utility.

Heterocyclic compounds can be synthesised by cyclisation reactions (accompanied by elemination of small molecules), addition reactions (adduct formation), ring transformation reactions or replacement involving groups. Formation of heterocycle from acyclic compounds alters the reactivity. Piperidine is reactive than ethyl propylamine due to the reduction in steric incumbrance of the nitrogen lone pair.

AIMS AND OBJECTIVES

In the pharmaceutical field, there is a need for new and novel chemical inhibitors of biological functions. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesising pharmacologically interesting heterocyclic compounds of widely different composition.

During the course of research work looking to the applications of heterocyclic compounds, several entities have been designed, generated and characterised using spectral studies. The aims and objectives of the work carried out are as under.

1. To synthesise pharmacologically active entities like pyrazolines, oxopyrimidine, thiopyrimidine, cyanopyran barbitones, aminopyrimidine, cyanopyridine, and thiosemicarbazones, acetonitrile, azomethine and thiazolidinone bearing 1,N-Phenyl-3-â-pyridyl pyrazole nucleus.

2. To characterise these products for structural elucidation using spectroscopic techniques like IR, PMR and Mass spectral studies.

3. To check the purity of all compounds using thin layer chromatography.

4. To evaluate these new products for better drug potential against different strains of bacteria, fungi and for antitubercular activity.

The research work is presented as studies on [A] Chalcones and [B] Pyrazoles.

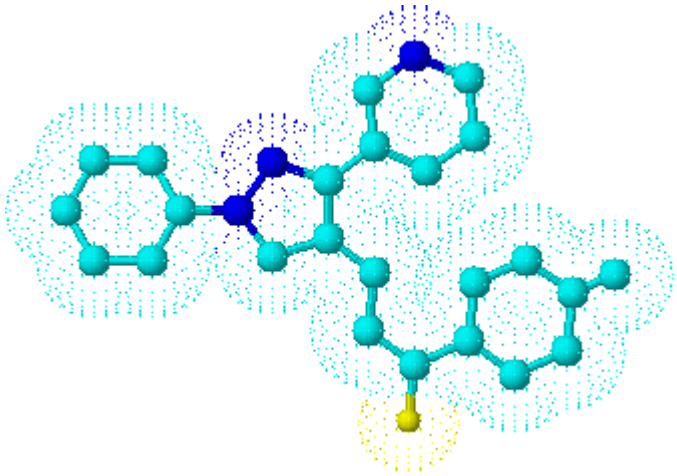
In a programmed research directed towards the construction of therapeutically active new heterocycles bearing 1,N-Phenyl-3-â-pyridyl pyrazole nucleus has been investigated in following parts.

[A] STUDIES ON CHALCONES

PART - I : STUDIES ON PYRAZOLINES
PART - II : STUDIES ON PYRIMIDINES
PART - III : STUDIES ON CYANOPYRANS
PART - IV : STUDIES ON BARBITONES
PART - V : STUDIES ON AMINOPYRIMIDINES
PART - VI : STUDIES ON CYANOPYRIDINES
PART - VII : STUDIES ON THIOSEMICARBAZONES

[B] STUDIES ON PYRAZOLES

PART - VIII : STUDIES ON α-ARYLAMINONITRILES
PART - IX : STUDIES ON N-ARYL-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINES
PART - X : STUDIES ON THIAZOLIDINONES



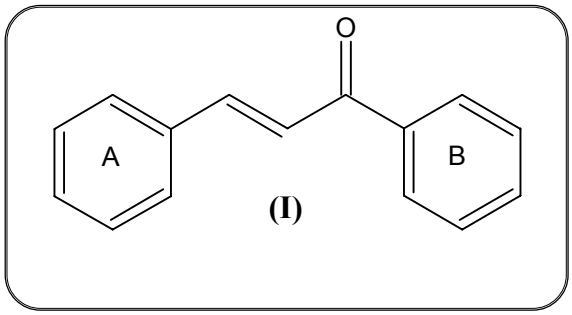
[A]

STUDIES ON CHALCONES

INTRODUCTION

The chemistry of chalcones have generated intensive scientific studies throughout the world, specially interesting for there their biological and industrial applications. Chalcones are coloured compounds because of the presence of the chromophore and auxochromes. They are known as *benzalacetophenones* or *benzylidene acetophenones*. Kostanecki and Tambor[1] gave the name *Chalcone.*

Chalcones are characterized by their possession of a structure in which two aromatic rings A and B are linked by an aliphatic three carbon chain.



(I)

The alternative names given to chalcones are phenyl styryl ketones, beanzalacetophenone, β-phenyl acrylphenone, γ-oxo-α,γ-diphenyl-α-propylene and α-phenyl-β-benzoethylene.

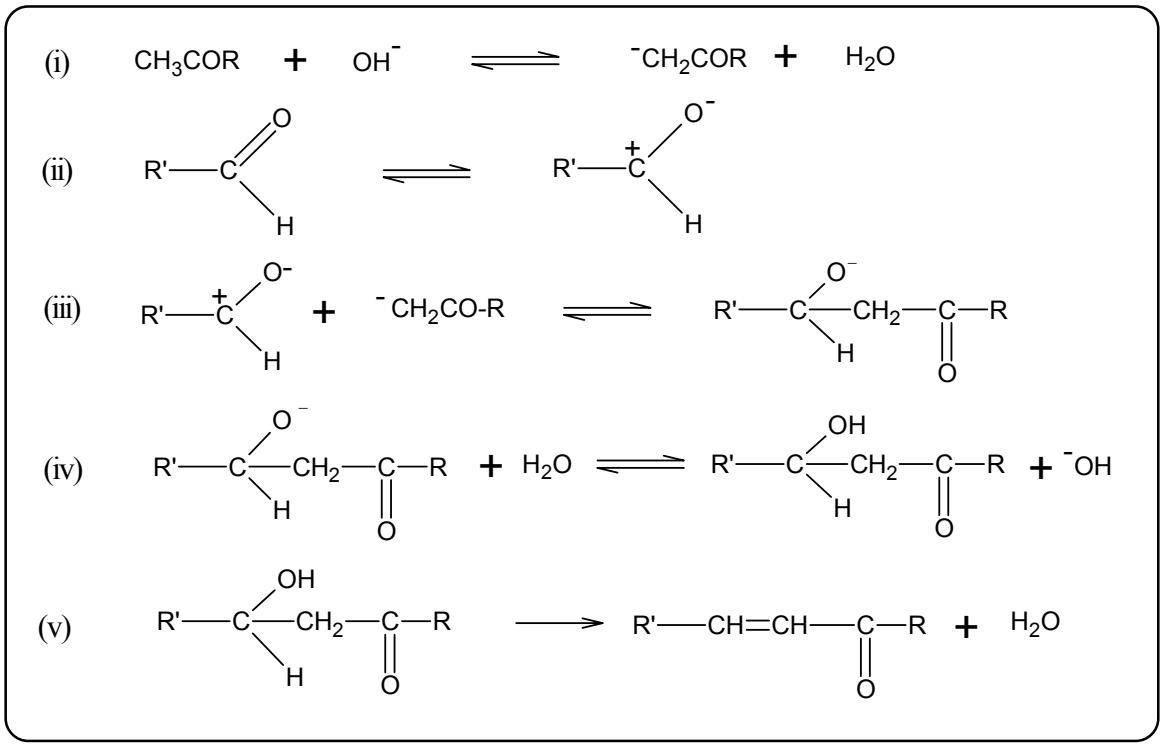
SYNTHETIC ASPECT :

A considerable variety of methods are available in literature for the synthesis of chalcones. The most convenient method is the one, that involves the Claisen-Schimidt condensation of equimolar quantities of an aryl methyl ketones with arylaldehyde in presence of alcoholic alkali.[2]

Several condensing agents used are alkali of different strength[3,4] hydrochloric acid,[5,6] phosphorous oxychloride,[7] piperidine,[8] anhydrous aluminium chloride,[9] boron trifluoride,[10] aqueous solution of borax,[11] amino acids,[12] perchloric acid[13] etc.

MECHANISM :

Chalcone formation proceeds through Aldol type condensation and the process is catalyzed by the presence of alkali.[14] Following are the steps of the reaction mechanism.



The intermediate Aldol type products formed readily undergoes dehydration even under mild condition, particularly when R and R' are aryl groups.

REACTIVITY OF CHALCONES :

The chalcones have been found to be useful for the synthesis of variety of heterocyclic compounds are as under.

(a) Chalcones with monoethanolamine in ethanol gives 1,4-oxazipines.[15]

(b) Chalcones with 2-amino thiophenol in acetic acid produces 1,5-thiazepines.[16]

(c) Chalcones on reaction with semicarbazide hydrochloride in ethanol affords 1-carboxamide pyrazolines.[17]

(d) Chalcones on reaction with 2-aminopyridine in glacial acetic acid affords pyridopyrimidines.[18]

(e) Oxirane[19] can be prepared by the reaction of chalcone with H_2O_2 in basic media.

(f) Cyanopyridone[20] derivatives can be prepared by the condensation of chalcone with ethyl cyanoacetate.

(g) Chalcones on reaction with barbituric acid gave barbitone[21] derivatives.

(h) Chalcone gives imine derivatives with amine in presence of sulfuric acid as catalyst.[22]

(i) Pyrazolines[23] and its derivatives can be prepared by the condensation of chalcones with hydrazine hydrate and acetic acid.

(j) Chalcones on condensation with malononitrile and ammonium acetate yields 2-amino-3-cyano pyridines.[24]

(k) Isoxazoles[25] can be prepared by the treatment of chalcones with hydroxylamine hydrochloride and sodium acetate.

(l) Chalcones on condensation with malononitrile in pyridine forms 2-amino-3-cyano-pyrans.[26]

(m) Chalcones on treatment with urea in presence of alkali affords 2-oxopyrimidines.[27]

(n) Chalcones on reaction with thiourea in presence of alkali/acid yields 2-thienopyrimidines.[28]

(o) Chalcones on treatment with guanidine hydrochloride in presence of alkali affords 2-amino pyrimidines.[29]

(p) Chalcones react with P_2S_5 yielded 2-isothiazolidines.[30]

(q) Chalcones react with sodium nitrile in presence of glacial acetic acid in ethanol produces 2-1H-pyrimidines.[31]

THERAPEUTIC INTEREST :

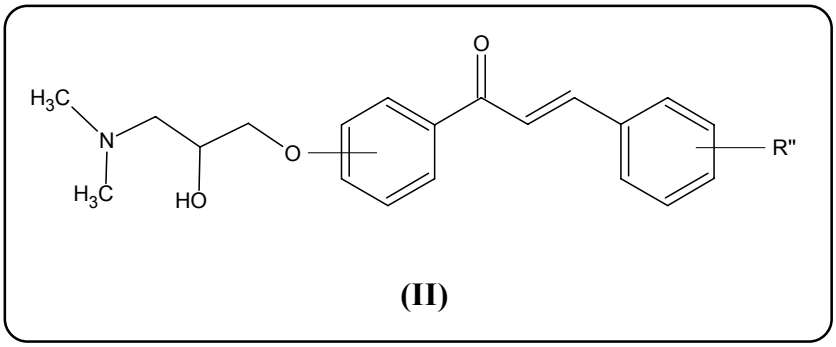
Chalcones are potential biocides, some naturally occurring antibiotics and amino chalcones probably own their biological activity due to the presence of α,β-unsaturated carbonyl group. Few of them are as below.

1. Antiallergic[32]
2. Carboxygenase inhibitor[33]
3. Antitumor[34,35]
4. Antimalarial[36]
5. Anticancer[37]
6. Antileishmanial[38]
7. Insecticidal[39,40]
8. Antiulcer[41]
9. Antiinflammatory[42,43]
10. Bactericidal[44,45]
11. Fungicidal[46,47]
12. Antiviral[48]
13. Anthelmintics[49]

Recently Ni Liming et. al.[50] have synthesized chalcones and screened for their antiinflammatory and cardiovascular activity. Kumar Srinivas et. al.[51] have synthesized chalcones as a antitumor agent. Ko Horng-Huey et. al.[52] have prepared chalcones as antiinflammatory agent. Nakahara Kazuhiko et. al.[53] have synthesized chalcones as carcinogen inhibitors. Antitubercular agents of chalcone derivatives have been prepared by Lin Yuh-Meei et. al.[54]

Ezico et. al.[55] have demonstrated that chalcone possess a valuable antiproliferation activity both on sensitive cancereous cell and on cell which are resistant to common chemotherapeutic drugs. Some of the chalcones have been patented for their use for treatment of glucoma[56] and showed antifungal[57,58] aldose reductase inhibitors,[59] anticancer[60] and antimicrobial[61,62] activities.

Das B. P. et. al.[63] have found that chalcones possesses larvicidal properties. Kim Min-Young et. al.[64] have synthesized chalcones and tested for their matrix metalloproteinase inhibitor activity. Satyanarayana M. et. al.[65] have synthesized chalcone derivatives as antihyperglycemic activity(II).

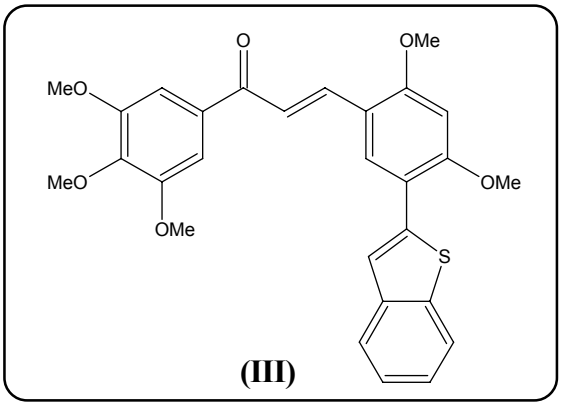


(II)

Moreover, synthesis and antibacterial activity of substituted chalcone derivatives have been reported by Modi et. al.[66] and Attia A.[67] V. Mudalir et. al.[68] have prepared phenoxychalcones and observed their insecticidal activity, Kammei et. al.[69] have synthesized chalone derivatives having antitumor activity. De Vincenzo et. al.[70] and Han et. al.[71] have reported chalcone derivatives for their antiinflammatory activity.

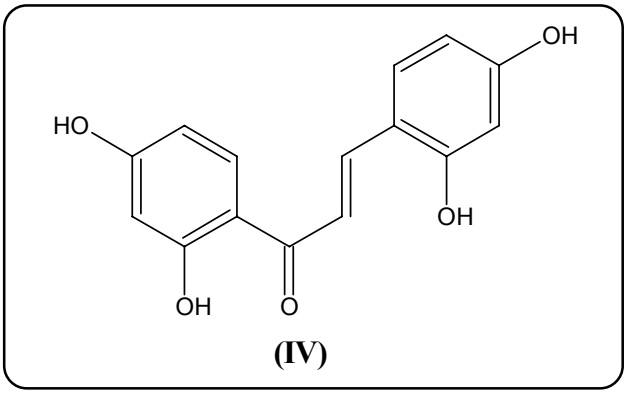
Aldose reductase inhibitor activity of chalcone derivatives have been reported by Okuyama et. al.[72] They are also associated with antitumor and antifungal activity as reported by A. Tsotitns and coworkers.[73] Antifeedant activity of chalcones have been observed by Sharma and Sreenivasulu.[74]

Liu Mei et. al.[75] have prepared antimalarial chalcones. Opletalova Veronika et. al.[76] have synthesized chalcones and screened as cardiovascular agents. Moreover, it has been found that chalcone derivatives possesses nitric oxide inhibitor,[77,78] anti HIV[79,80] and antiproliferative[81,82] activities. Meng C. Q. et. al.[83] discovered some novel heteroaryl substituted chalcones as inhibitors of TNF-alpha-induced VCAM-1 expression(III).



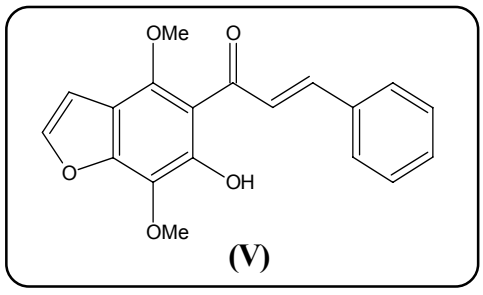
(III)

Moreover, Khatib S. et. al.[84] synthesized some novel chalcones as potent tyrosinase inhibitors(IV). Ko H. H. et. al.[85] have prepared some new chalcones for potent inhibition of platelet aggregation. Ziegler H. L. et. al.[86] reported some chalcones as antiparasitic. Go M. L. et. al.[87] have described the synthesis and biological activities of chalcones as antiplasmodial. Xue C. X. et. al.[88] synthesized chalcones as antimalarial agents. Fu Y. et. al.[89] have synthesized Licochalcone-A.



(IV)

Furthermore, Alcaraz M. J. et. al.[90] have described the role of nuclear factor kappaB and heme oxygenase-1 in the action of an anti-inflammatory chalcone derivative in RAW 264.7 cells. Nerya O. et. al.[91] have prepared some new chalcones as potent tyrosinase inhibitors.

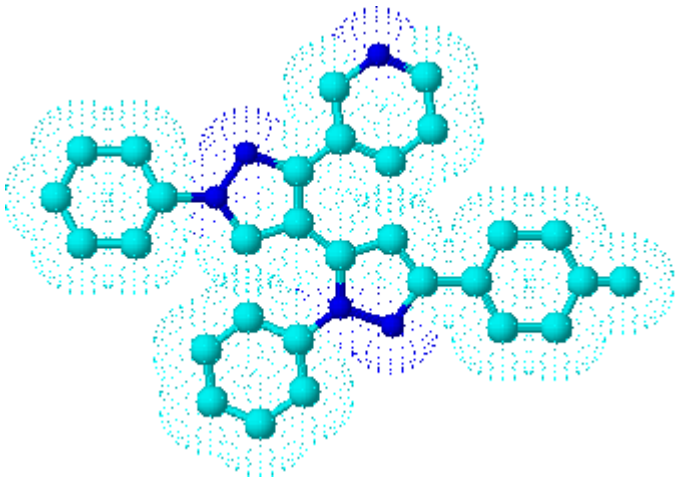


(V)

Sabzevari O. et. al.[92] have constructed some new chalcone derivatives as Molecular cytotoxic mechanisms of anticancer hydroxychalcones(V).

Recently, Ban H. S. et. al.[93] have synthesized some novel chalcones as inhibition of lipopolysaccharide-induced expression of inducible nitric oxide synthase and tumor necrosis factor-alpha by 2'-hydroxychalcone derivatives in RAW 264.7 cells. Hollosy F. et. al.[94] have prepared some new chalcones as Plant-derived protein tyrosine kinase inhibitors as anticancer agents.

These valid observation led us to explore chalcone chemistry by synthesizing several derivatives like pyrazolines, oxopyrimidines, thiopyrimidines, cyanopyrans, barbitones, aminopyrimidines, cyanopyridine and thiosemicarbazones bearing different heterocyclic ring systems for medicinal value, in order to achieving better therapeutic agents, this study described as under.

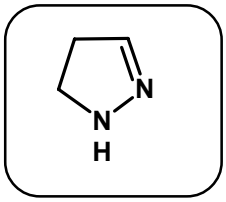


PART - I

STUDIES ON PYRAZOLINES

INTRODUCTION

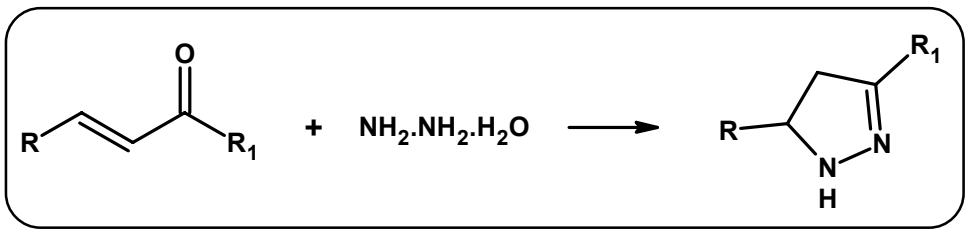
Amongst nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful framework for biological activities, pyrazolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. In 1967 Jacobe, reviewed the chemistry of pyrazolines, which have been studied extensively for their biodyndmic behaviour[98] and industrial applications[99].



SYNTHETIC ASPECT :

Different methods for the preparation of 2-pyrazoline derivatives documented in literature are as follows.

1. 2-Pyrazolines can be constructed by the cyclocondensation of chalcones with hydrazine hydrate[100].

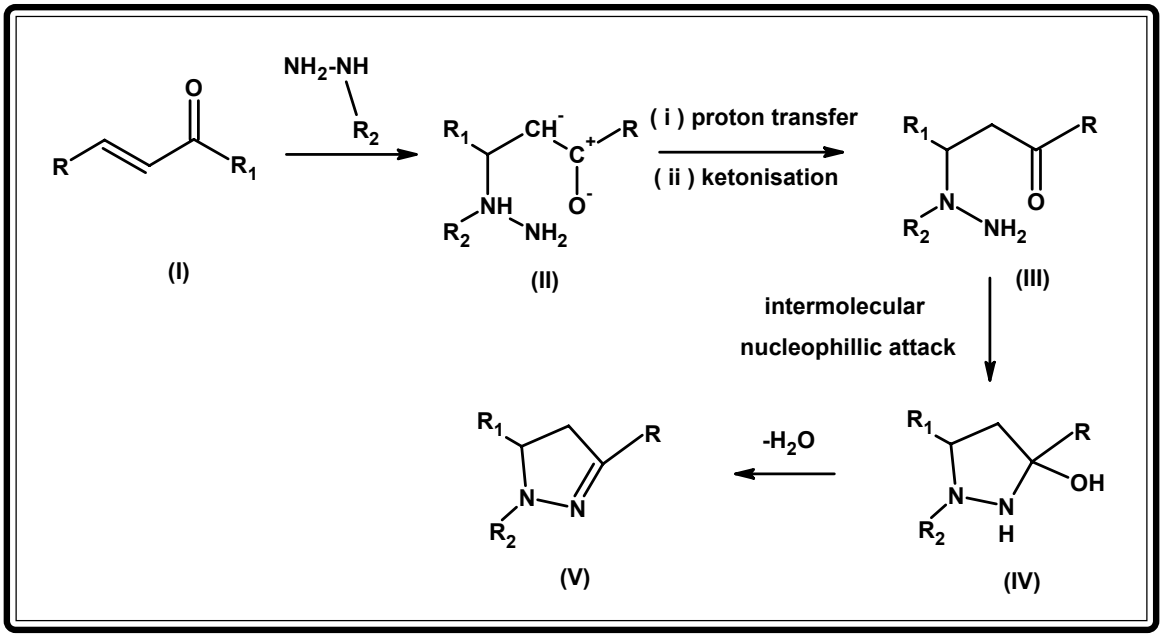


2. 2-pyrazolines can also be prepared by the condensation of chalcone dibromide with hydrazines[101].
3. 2-pyrazolines can be synthesised by the cycloaddition of diazomethane to substituted chalcones[102].
4. Dipolar cycloaddition of nitrilimines of dimethyl fumarate, fumaronitrile and the N-aryl maleimides yields the corresponding pyrazolines[103].
5. Epoxidation of chalcones have epoxy ketones which reacted with hydrazine and phenyl hydrazine to givepyrazolines[104].

Further more, B. Gyassi et. al.[105] investigated the one pot synthesis of some pyrazolines in dry media under microwave irradiation. S. Paul et. al.[106]and Dandia Anshu et. al.[107] have also described the microwave assisted synthesis of 2-pyrazolines.

MECHANISM

The following mechanism seems to be operable for the condensation of chalcones with hydrazine hydrate.[108]



Nucleophilic attack by hydrazine at the β-carbon of the α,β-unsaturated carbonyl system forms species (II), in which the -ve charge is mainly accomodated by the electronegative oxygen atom.

Proton transfer from the nitrogen to -ve oxygen produces an intermediate enol which simultaneously ketonises to ketoamine (III). Another intramolecular nucleophilic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to carbonyl amine (IV). The later with a hydroxy group and amino group on the same carbon lose water molecule to yield the pyrazolines.

THERAPEUTIC IMPORTANCE

From the literature survey, it was revealed that 2-pyrazolines are better therapeutic agents.

1. Analgesic[108,109]
2. Bactericidal[110,111]
3. Cardiovascular[112]
4. Diuretic[113]
5. Fungicidal[114]

6. Herbicidal[115]
7. Hypoglycemic[116]
8. Insecticidal1[117]
9. Tranquilizer[118]
10. Antiallergic[119]
11. Anticonvulsant[120,121]
12. Antidiabatic[122]
13. Antiimplantation[123]
14. Antiinflammatory[124]
15. Antitumor[125]
16. Antineoplastic[126]
17. Antimicrobial[127]

S. S. Sonarc et. al.[128] have synthesised-3-(2-acetoxy-4-methoxyphenyl)-5-(substituted phenyl)-pyrazolines and tested their antimicrobial activity. H. H.Parekh[129] et. al. have also synthesised some new pyrazolines as an antimicrobial agent. G. N. Mishirika et. al.[130] have also prepared 2-pyrazolines of salicyclic acid (II) possessing antimicrobial properties.

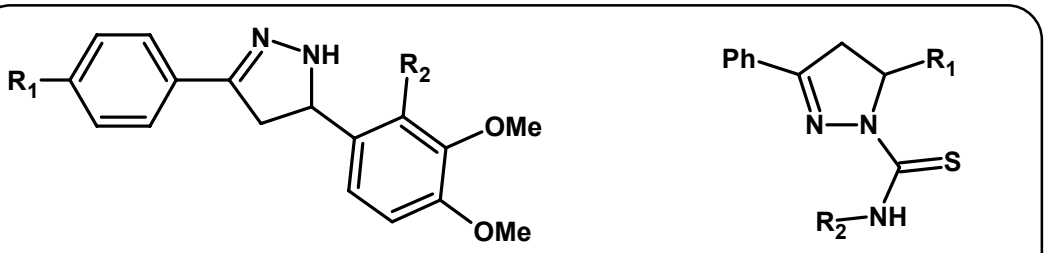
Tunfawy, Atif and co-workers[131] have patented 3-methyl-4'-(substituted phenylazo)-pyrazol-5-ones as antibacterial agents.

Moreover F. Manna and co-worker[132] have described 1-acetyl-5-(2'-bromophenyl)-4,5-dihydro-3-(2'-hydroxyphenyl)-1H-pyrazolines and its derivatives which acts as potent antiinflammatory, analgesic and antipyratic agents. Udupi R. H. and Bhatt A. R.[133] have reported the synthesis and biological activity of Mannich bases of certain 1,2-pyrazolines. Nugent Richard[134] investigated pyrazolines bis phosphonate ester as novel antiinflammatory and antiarthritic agent.

Fuche Rainer et. al.[135] have prepared some new 1H-pyrazoline derivatives and reported them as pesticides. Furthermore, Tsubai et. al.[136] have synthesised some new (phenylcarbamoyl) pyrazolines as an insecticides and at 40% concentration shows 100% mortality of spodopetra litura larve after seven drops.

Moreover, T. M. Stivensen et. al.[137]have also investigated N-substituted pyrazoline type insecticides. Tanka Katsohori[138] have patented pyrazoline derivatives as herbicides and Johannes et. al.[139] as insecticides. Moritaz Z. and Hadol[140] to investigated a semi emperial molecular orbital study on the reaction of aminopyrazolinyl azodye with singlet molecular oxygen.

Shivnanda M. K. and co-workers[141] have prepared substituted pyrazolines and reported their antibacterial activity. E. Palska et. al.[142] have prepared 3,5- diphenyl-2-pyrazolines (I) and cited their antidepressant activity.



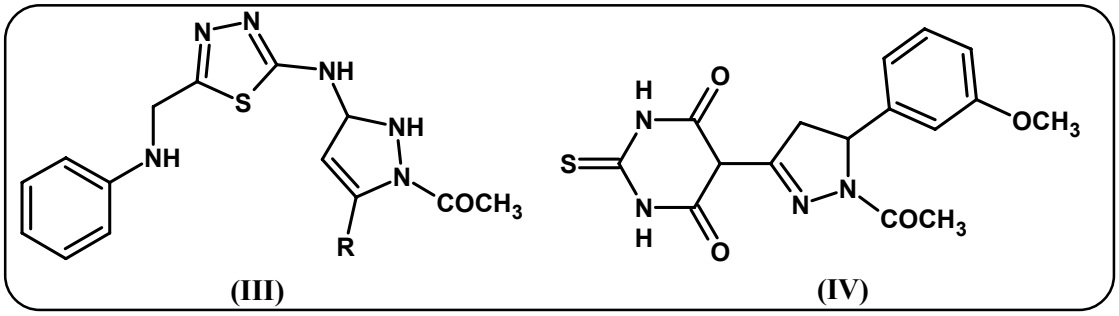
(I) R_1 =H, Cl, Br, Me, MeO
R_2 = H, Cl

(II) R_1, R_2 = Aryl

B. Shivrama et al.[143,144] have synthesised pyrazolines as antibacterial agents. Hiremath S. P. et. al.[145] have synthesised pyrazolines as analgesics antiinflammatory and antimicrobial agents. Malhotra V. et. al.[146] have synthesised new pyrazolines as a cardiovascular agents (II).

Almstead J. et. al.[147] have prepared pyrazolines as vascularization agents. Guniz Kuchkguzel et. al.[148] have synthesised pyrazolines as a antimicrobial and anticonvalsant agents. Gulhan T. Z. and co-workers[149] have prepared pyrazolines as a hypotensive agent. Shulabh Sharma et. al.[150] have synthesised pyrazolines and tested their antiinflammatory activity (III).

Ashok Kumar et. al.[151] have synthesised pyrazolines as anticonvulsant agents (IV). Maurer Fritz et. al.[152] have synthesised pyrazoles and screened for their pesticidal activity.

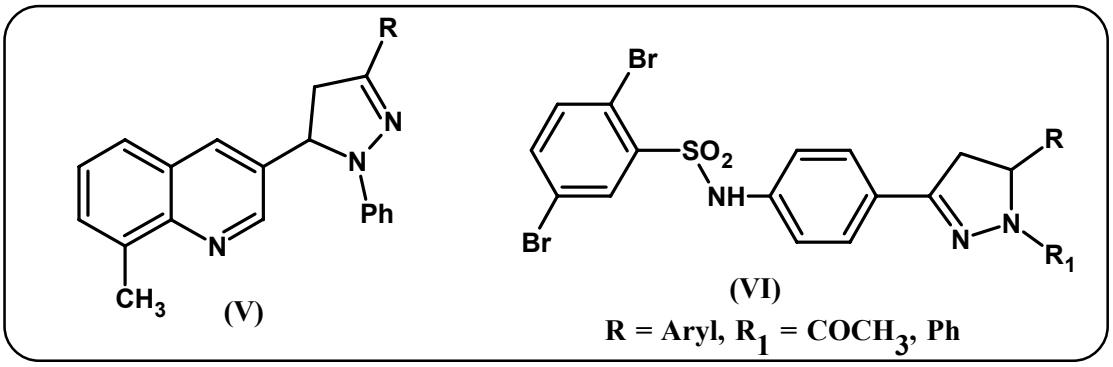


(III) (IV)

CONTRIBUTION FROM OUR LABORATORY

Parekh et. al.[153] have prepared 1-Acetyl-5-aryl-3-[3,-(3,4-dihydro-2-methyl-4-one-3-quinozalinyl)-phenyl]-2-pyrazolines which possess antimicrobial activity. Several pyrazolines bearing thymol moiety were evaluated for their ability as potent antimicrobial by Hansa Parekh et. al.[154] Parekh and co-workers[155] have prepared pyrazolines from arsanilic acid for their antimicrobial activity. Parekh et. al.[156,157] have synthesised and reported the antimicrobial activity of pyrazolines.

Parikh et. al.[158] have synthesised some antimicrobial pyrazolines. Parekh et. al.[159] have synthesised phenyl pyrazolines bearing quinoline (V) moiety and described their antimicrobial activity. Parikh et. al.[160] have synthesised and tested the antimicrobial activity of p-(2',5'-dibromo benzene sulphonamido)-phenyl-5-aryl-1H/acetyl/phenyl-2-pyrazolines (VI).



(V)

(VI)

R = Aryl, R_1 = $COCH_3$, Ph

Recently, A. R. Parikh and co-workers have synthesised newer pyrazolines [161-166] with variety of biological activity.

In view of therapeutic activities shown by pyrazolines, it was contemplated to synthesise some new pyrazolines in search of agents possessing higher biological activity with least side effect have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-β-PYRIDYL-4-FORMYL PYRAZOLE

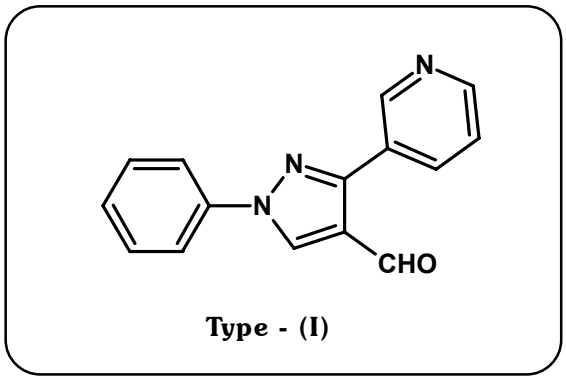
SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

SECTION - III: SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-PYRAZOLINES

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-β-PYRIDYL-4-FORMYL PYRAZOLE

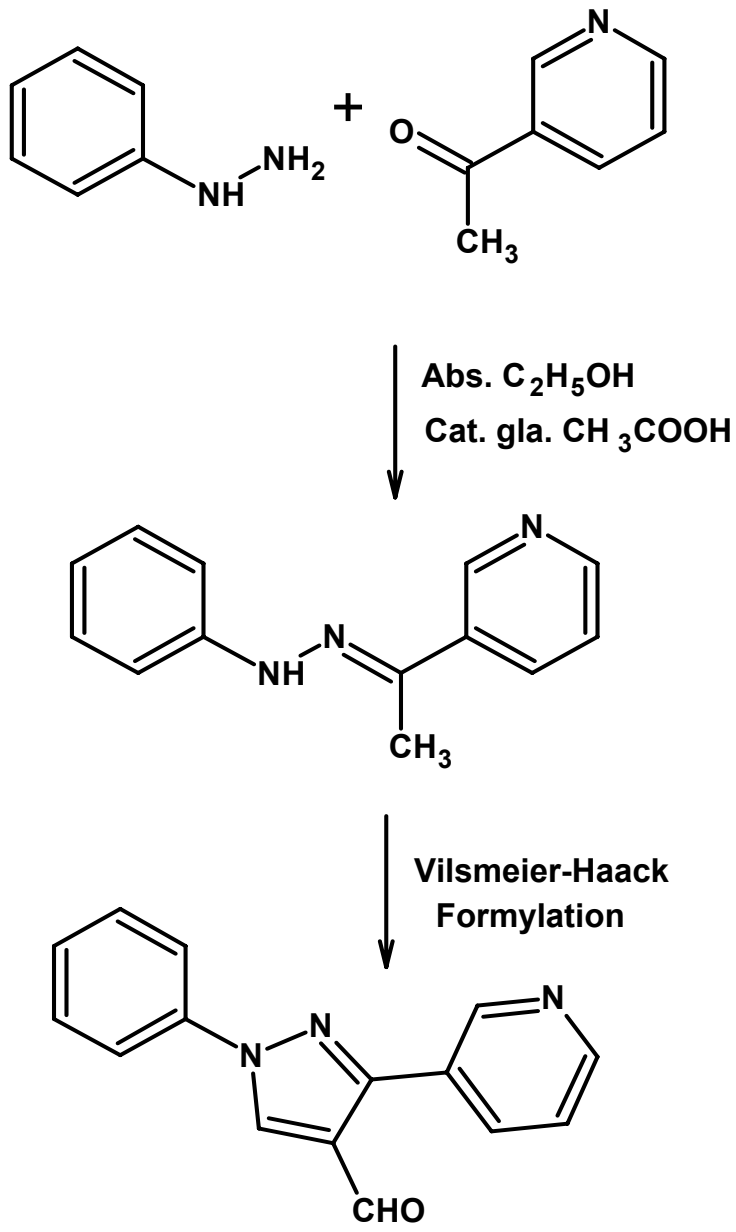
Recently, much interest has been focused on the synthesis and biodynamic behaviour of pyrazole aldehyde and it is a good synthon for various heterocyclic rings. With a view to obtaining compounds having better therapeutic activity, we have synthesised 1,N-Phenyl-3-β-pyridyl-4-formyl pyrazole by the condensation of 3-Acetyl pyridine phenyl hydrazone.



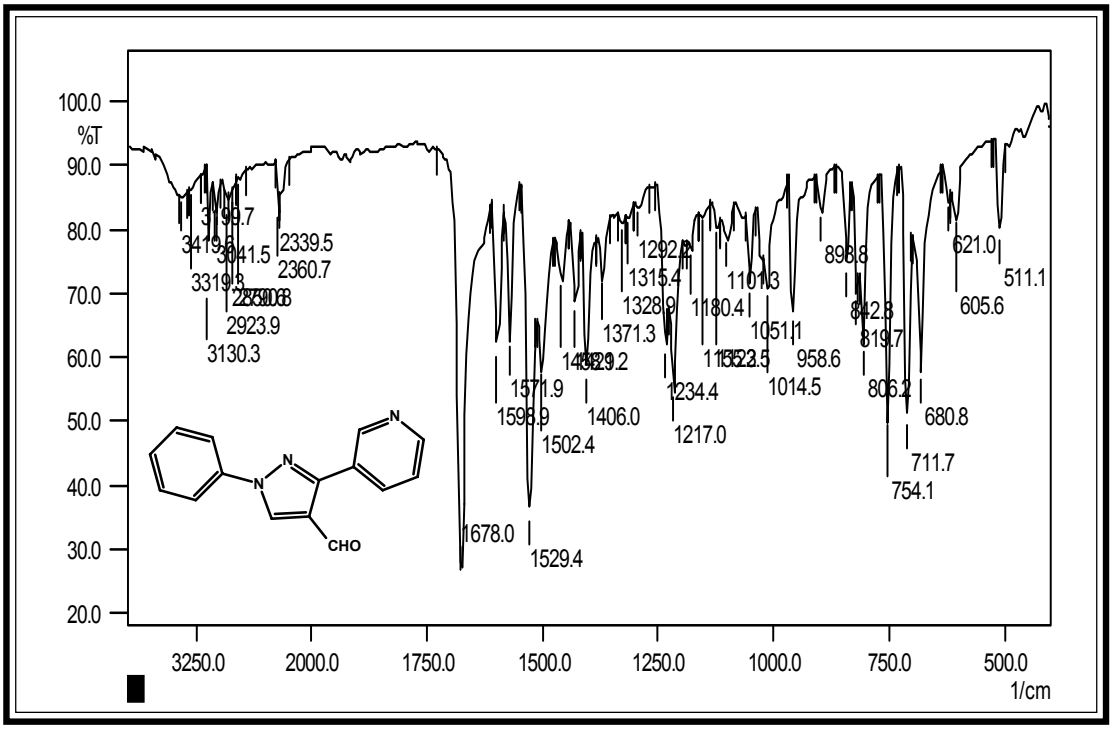
Type - (I)

The constitution of the synthesised product has been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectoscopy. The mass spectra of (1,N-Phenyl-3-β-pyridyl-4-formyl pyrazole) give m/z = 249 (recorded on Page No. 32). The fragmentation is also explained (Page No. 32).

REACTION SCHEME



IR SPECTRAL STUDY OF 1,N-PHENYL-3-β-PYRIDYL-4-FORMYL PYRAZOLE

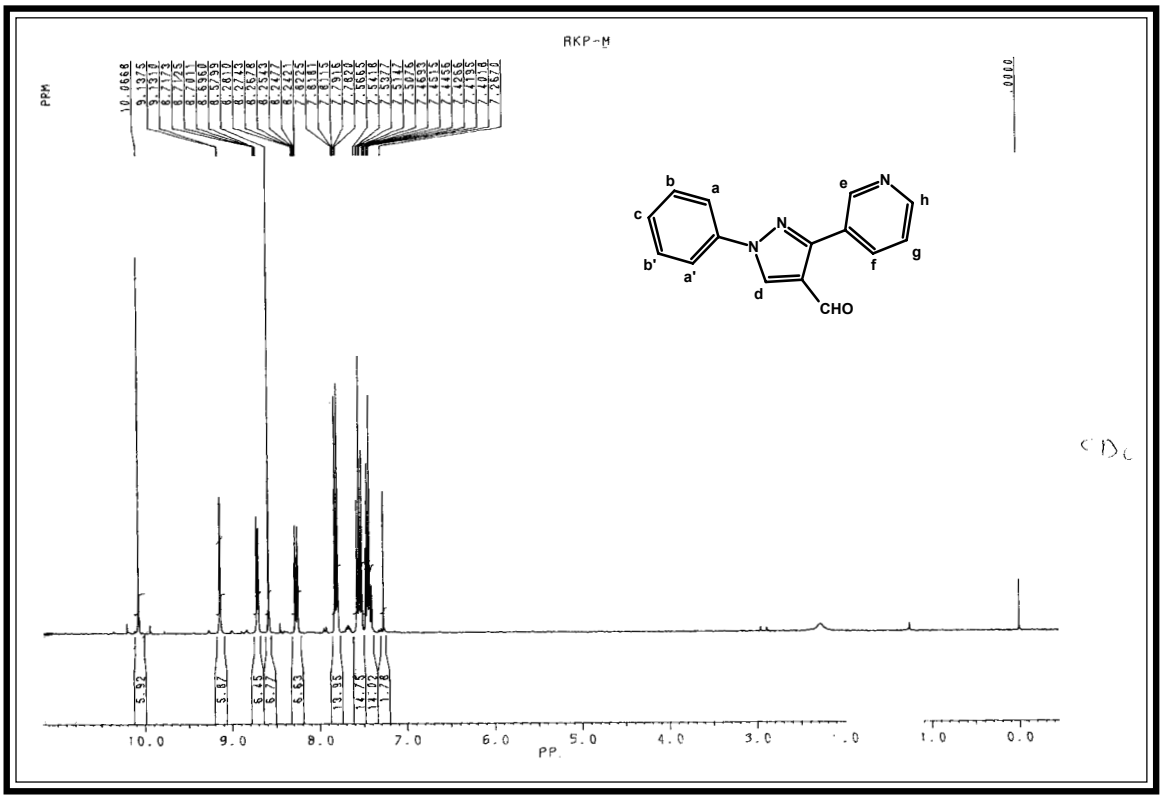


Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1}

(KBrDisc.)

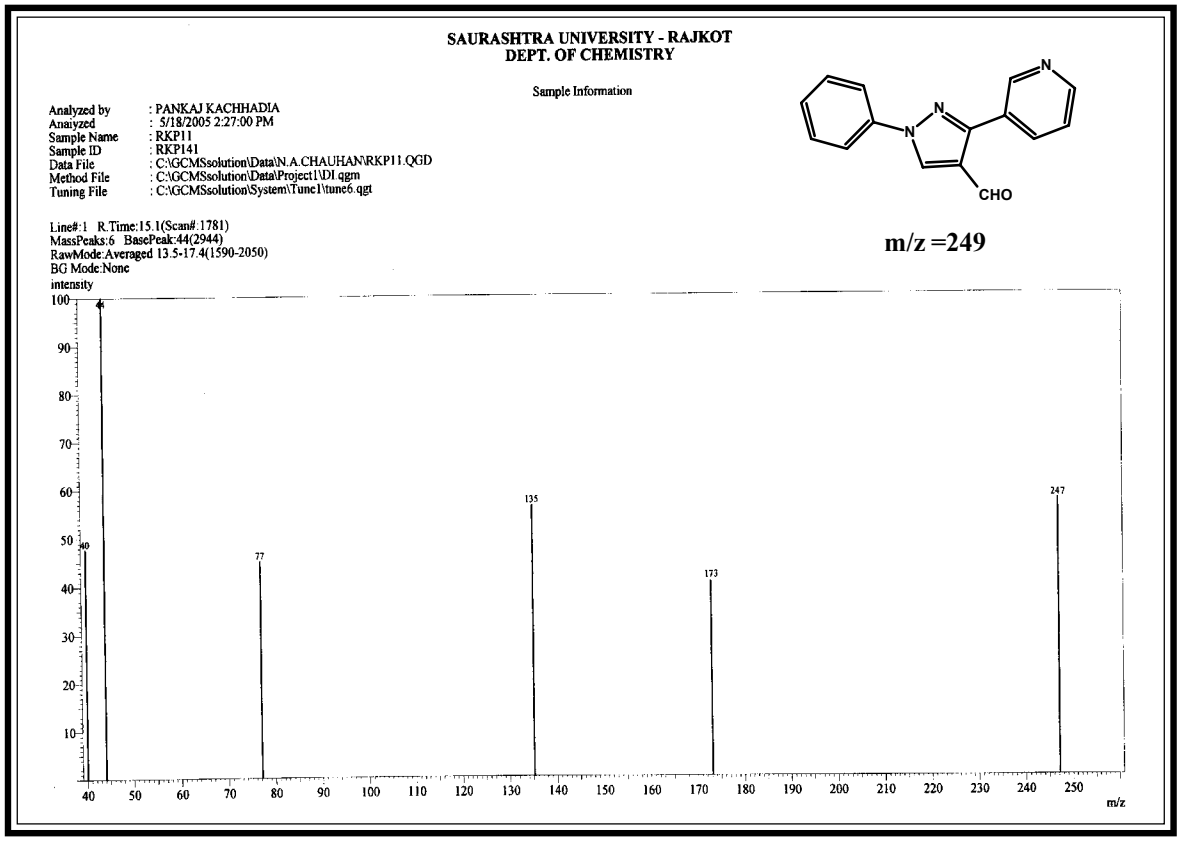
Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2925	95
-CH_3	C-H str. (sym.)	2850	2880-2850	,,
	C-H i.p.def. (asym.)	1429	1470-1435	,,
	C-H o.o.p. def. (sym.)	1371	1390-1370	,,
Aromatic	C-H str.	3141	3090-3030	96
	C=C str.	1502	1540-1480	,,
	C-H i.p. (def.)	1101	1125-1090	,,
	C-H o.o.p. (def)	1051	1070-1000	,,
Pyrazole	C=N str.	1598	1610-1590	96
moiety	C-N str.	1217	1230-1020	,,
Aldehyde	C=O str.	1678	1700-1640	95

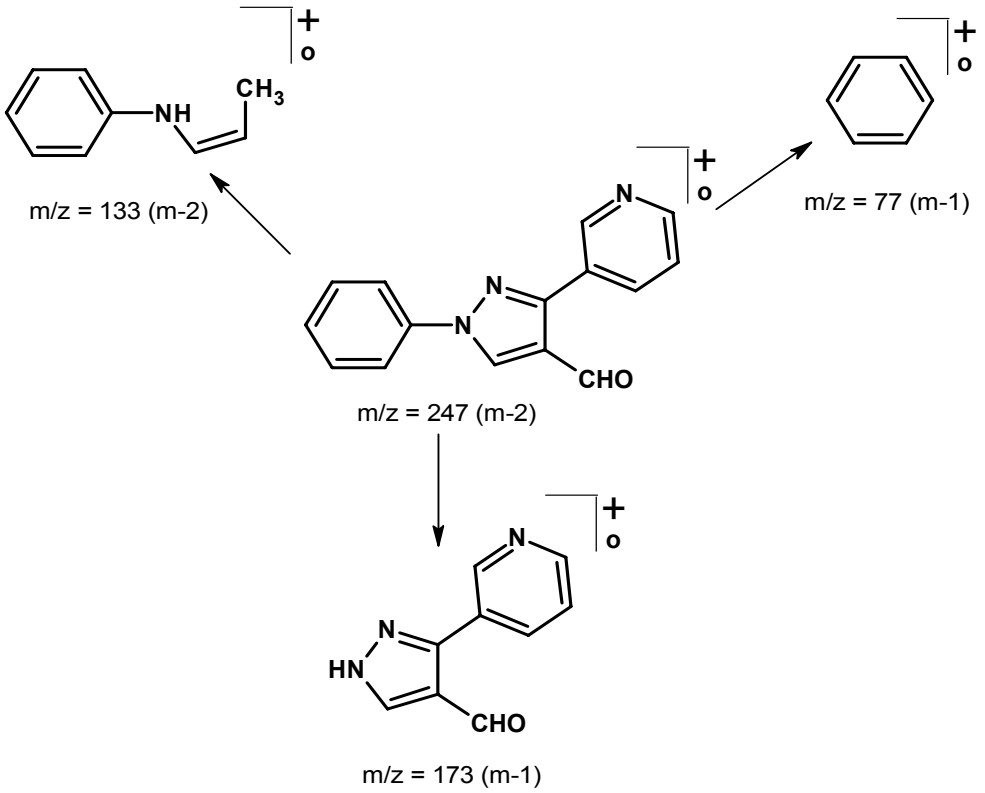
NMR SPECTRAL STUDIES OF 1,N-PHENYL-3-β-PYRIDYL-4-FORMYL PYRAZOLE



Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	7.40-7.45	2H	multiplet	Ar-Hc,f	-
2	7.50-7.53	2H	doublet	Ar-Hbb’	Jbb’=6.9
3	7.79-7.82	2H	doublet	Ar-Haa’	Jji=7.95
4	8.24-8.28	1H	multiplet	Ar-Hg	-
5	8.57	1H	singlet	Ar-Hd	-
6	8.69-8.71	1H	multiplet	Ar-Hh	-
7	9.13	1H	singlet	Ar-He	-
8	10.06	1H	singlet	-CHO	-


SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY
Sample Information
Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 5/18/2005 2:27:00 PM
Sample Name : RKP11
Sample ID : RKP141
Data File : C:\GCMSsolution\Data\N.A.CHAUHAN\RKP11.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune6.qgt
Line#:1 R.Time:15.1(Scan#:1781)
MassPeaks:6 BasePeak:44(2944)
RawMode:Averaged 13.5-17.4(1590-2050)
BG Mode:None
intensity
m/z
m/z =249


m/z = 133 (m-2)
m/z = 77 (m-1)
m/z = 247 (m-2)
m/z = 173 (m-1)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-β-PYRIDYL-4-FORMYL PYRAZOLE

[A] Synthesis of 3-Acetyl pyridine phenyl hydrazone

A mixture of phenylhydrazine (1.08 g, 0.01 M) and 3-acetylpyridine (1.2 g, 0.01 M) in absolute ethanol was refluxed in water bath for 12hrs. in the presence of glacial acetic acid (1 ml). The crude product was crystallised from absolute alcohol. Yield 85%; m.p. 108^{o}C; (Anal. calcd. for $C_{13}H_{13}N_3$; Required: C, 73.91; H,6.20; N,19.89 %; Found: C, 73.81; H, 6.11; N,19.78 %).

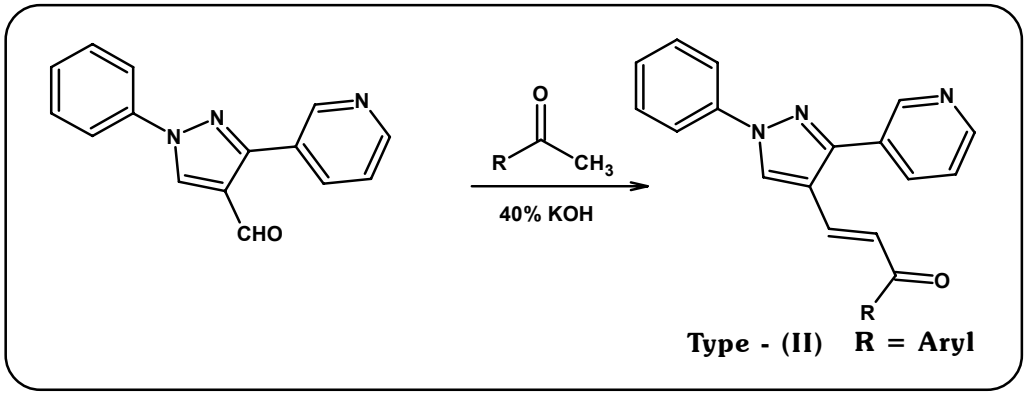
[B] Synthesis of 1-Phenyl-3-β-pyridyl-4-formyl pyrazole

3-Acetyl pyridine phenyl hydrazone (0.844 g, 0.004 M) was added to Vilsmeier-Haack reagent (prepared by dropwise addition of 1.2 ml $POCl_3$ in ice cooled 10 ml DMF) and refluxed for 5 hrs. The reaction mixture was poured on to crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from ethanol. Yield, 80%; m.p. 154^{o}C; (Anal. calcd. for $C_{15}H_{11}N_3O$; Required: C,72.28; H,4.45; N,16.86 % Found : C,72.16 ; H,4.34; N,16.73%).

SECTION - II

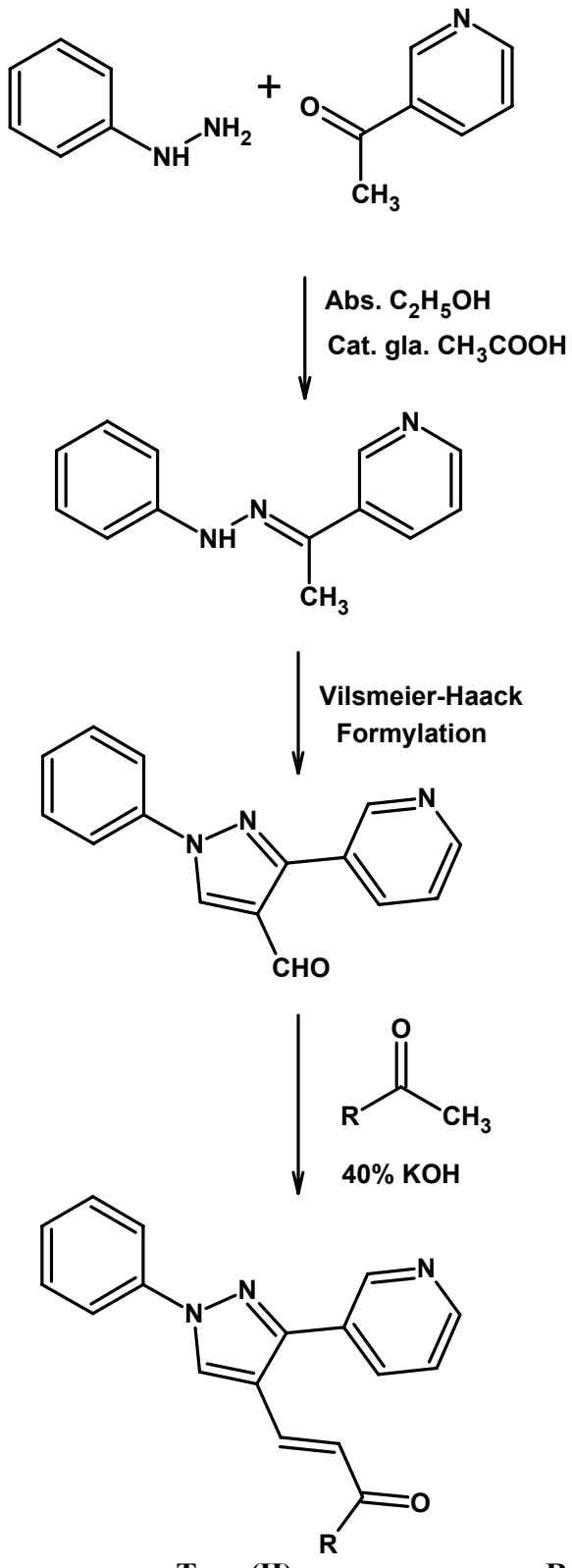
SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

With the biodynamic activities of chalcones and it is a good synthon for various heterocyclic rings, the interest has been focussed on the synthesis of new chalcones. With a view to obtained compounds having better therapeutic activity, we have synthesized 1-Aryl-3-(1'N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-ones by the condensation of 1N-phenyl-3-β-pyridyl-4-formyl pyrazole with various aromatic ketones in presence of catalyst of alkali.



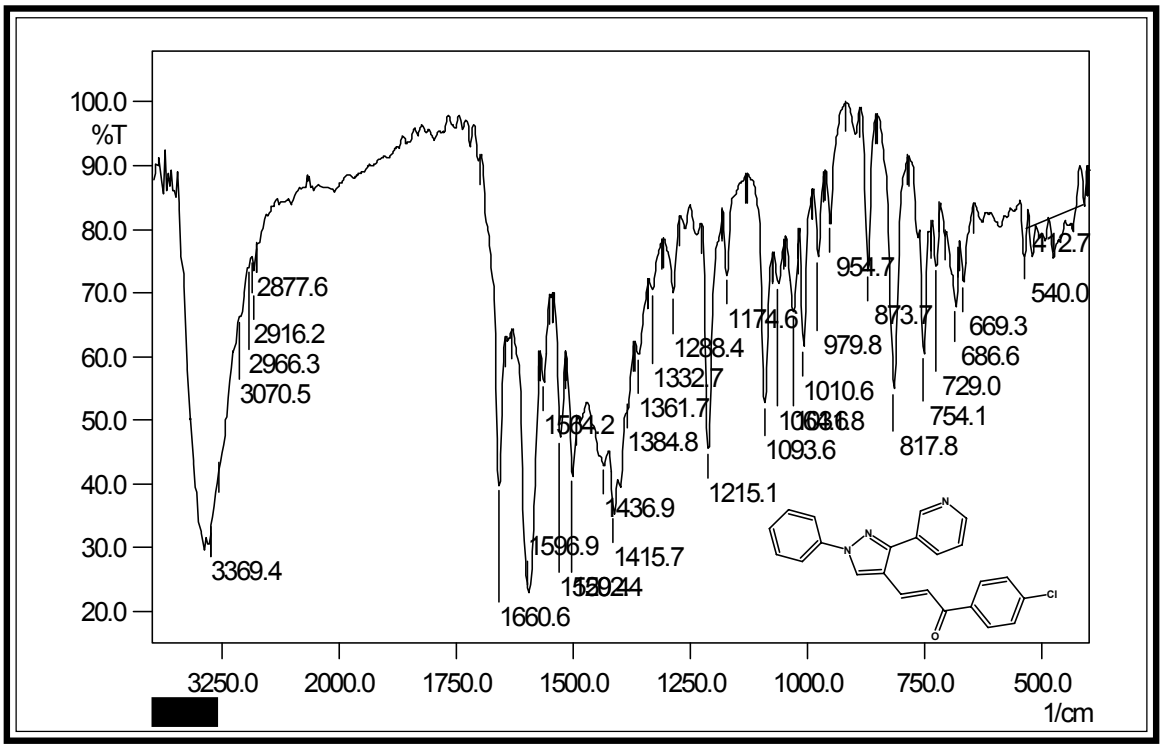
The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy. The mass spectra of 1-(p-Bromophenyl)-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-one give m/z = 428 (recorded on Page No. 38). The fragmentation is also explained (Page No. 39).

Reaction Scheme



Type-(II) **R = Aryl**

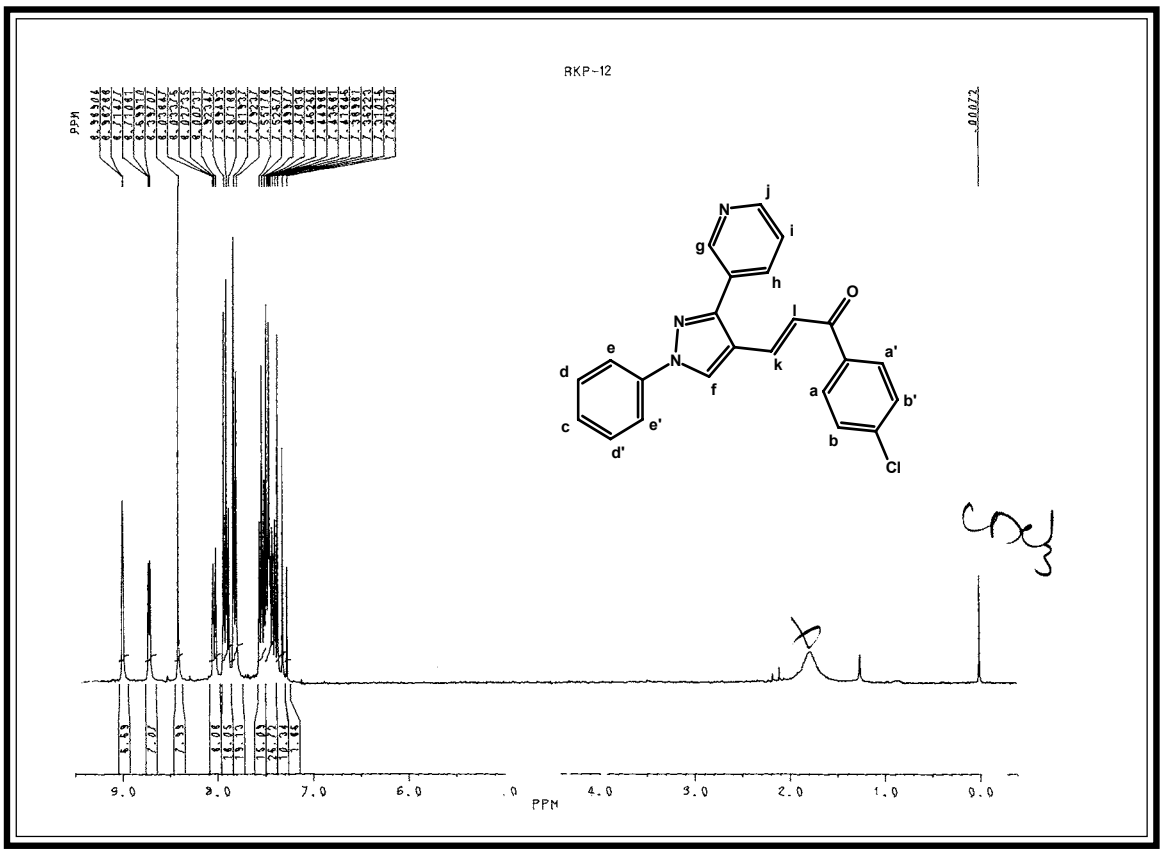
IR SPECTRAL STUDY OF 1-(p-CHLOROPHENYL)-3-[1',N-PHENYL-3'-β-PYRDIYL-PYRAZOL- 4'-YL]-2-PROPEN-1-ONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1}(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2966	2975-2950	95
-CH_3	C-H str. (sym.)	2877	2880-2860	,,
	C-H i.p.def. (asym.)	1436	1470-1435	,,
	C-H o.o.p. def. (sym.)	1384	1390-1370	,,
Aromatic	C-H str.	3070	3090-3030	96
	C=C str.	1502	1540-1480	,,
	C-H i.p. (def.)	1093	1125-1090	,,
	C-H o.o.p. (def)	1031	1070-1000	,,
Pyrazole	C=N str.	1596	1610-1590	96
moiety	C-N str.	1215	1230-1020	,,
α,β-unsaturated	C=O str.	1660	1700-1640	95
ketone	CH=CH str.	1502	1644-1618	,,
	C-H wag.	979	980-965	,,
Halogen	C-Cl str.	686	600-800	,,

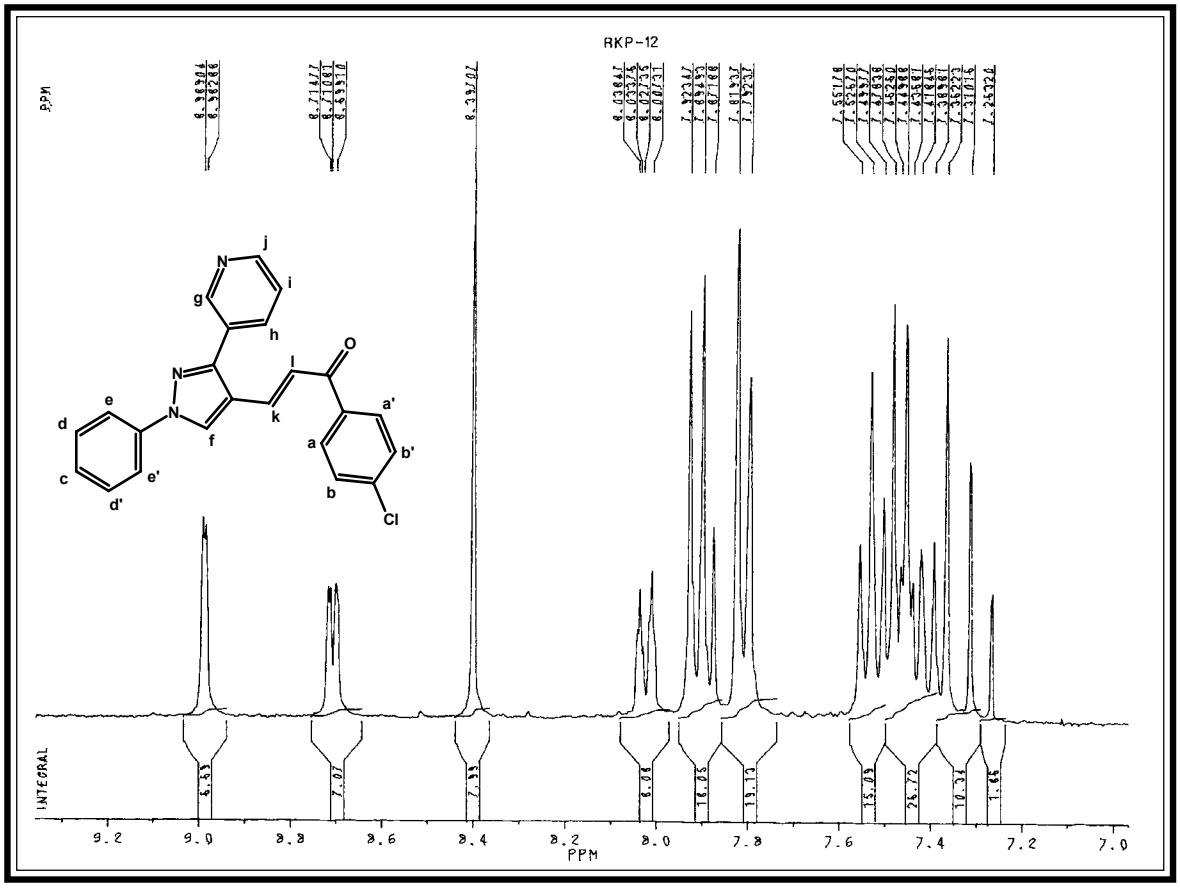
NMR SPECTRAL STUDIES OF 1-(p-CHLOROPHENYL)ARYL-3-[1',N-PHENYL-3'-β-PYRDIAYL-PYRAZOL- 4'-YL]-2PROPEN-1-ONE

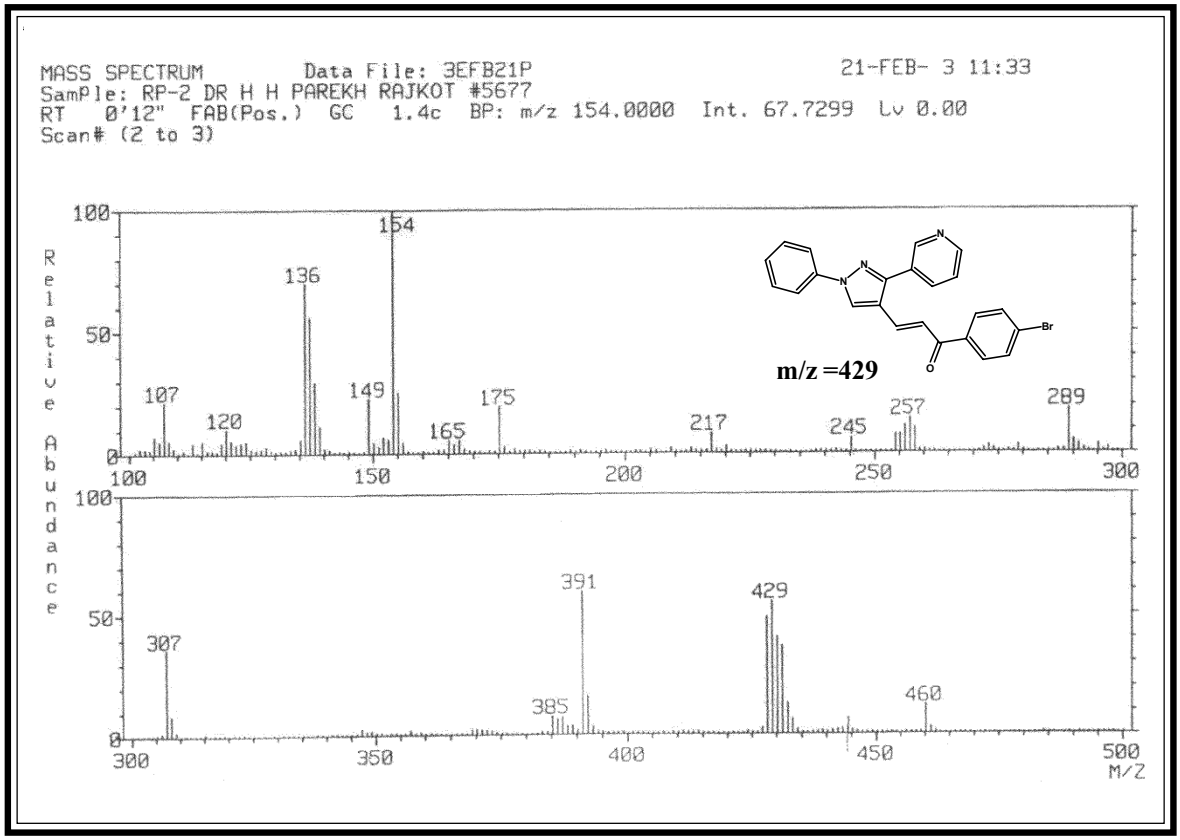


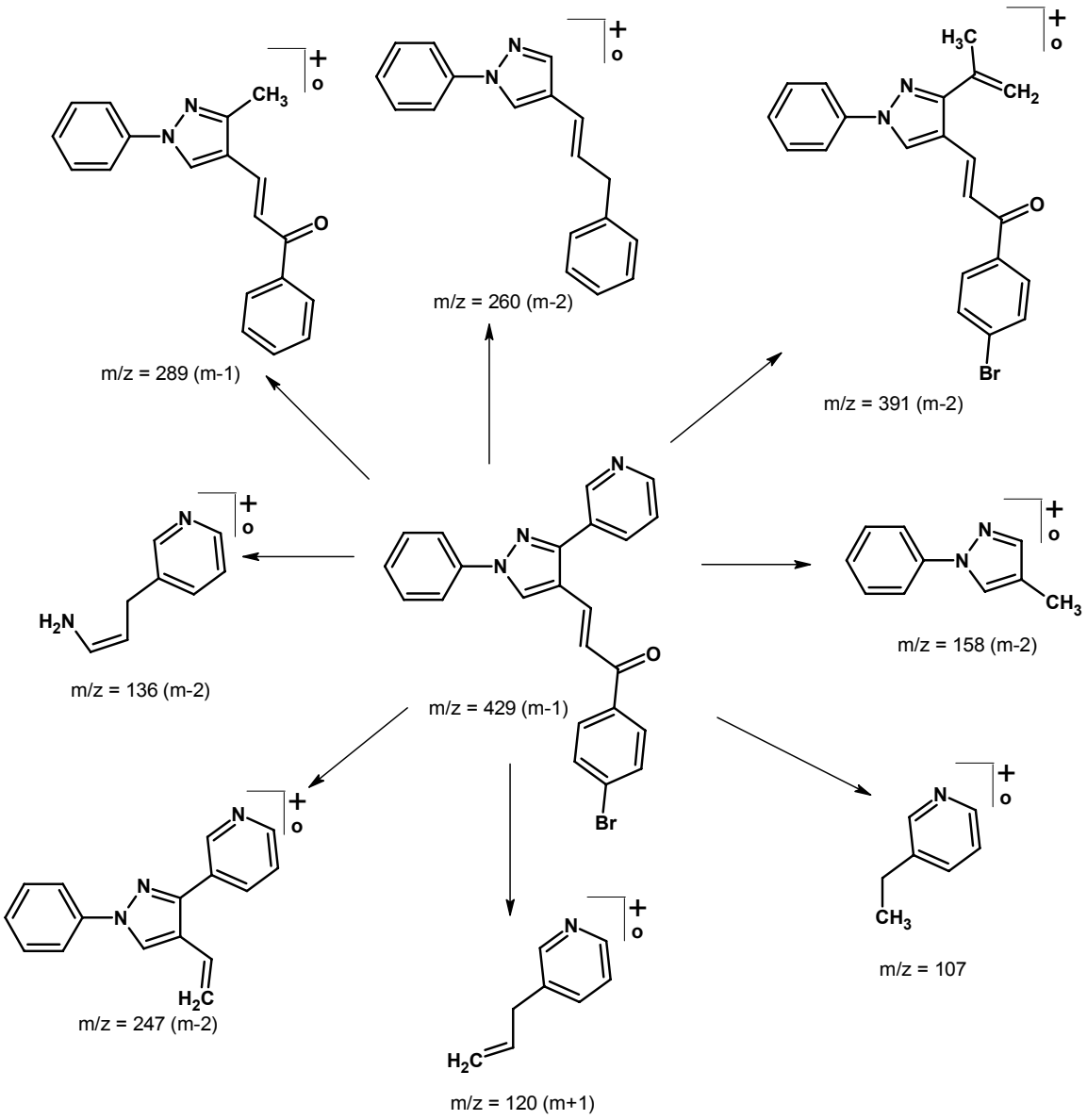
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	7.31-7.36	1H	doublet	Vin.Hm	Jml=15.6
2	7.41-7.47	4H	multiplet	Ar-Ha,a',c,h	-
3	7.52-7.53	2H	doublet	Ar-Hdd'	Jdd'=7.52
4	7.79-7.81	2H	doublet	Ar-Hbb'	Jbb'=8.1
5	7.89-7.92	2H	doublet	Ar-Hee'	Jee'=8.6
6	7.87-7.92	1H	doublet	Vin.Hl	Jlm=15.5
7	8.0-8.3	1H	doublet	Ar-Hj	Jjk=7.93
8	8.39	1H	singlet	Ar-Hf	-
9	8.70-8.72	1H	doublet	Ar-Hk	Jkj=6.00
10	8.98	1H	singlet	Ar-Hg	-

EXPANDED AROMATIC REGION






m/z = 289 (m-1)
m/z = 260 (m-2)
m/z = 391 (m-2)
m/z = 136 (m-2)
m/z = 158 (m-2)
m/z = 429 (m-1)
m/z = 247 (m-2)
m/z = 107
m/z = 120 (m+1)

ANTIMICROBIAL ACTIVITY

Method	:	Cup-Plate[97]
Gram positive bacteria	:	***B. cocous and B. subtillus***
Gram negative bacteria	:	***Proteus vulgaris***
		Escherichia coli
Fungi	:	***Aspergillus niger***
Concentration	:	40 mg
Solvent	:	Dimethyl formamide
Standard drug	:	Amoxycillin, Benzoylpenicillin,
		Ciprofloxacin, Erythromycin, Greseofulvin.

The antimicrobial activity was compared with standard drugs viz. Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin, and antifungal activity was compared with viz Greseofulvin. The zone of inhibition measured in mm.

ANTITUBERCULAR ACTIVITY

The antitubercular activity was carried out at Tubrerculosis Antimicrobial Acquisition and Co-ordinating Facility (TAACF) U.S.A.

Method	:	BACTEC 460 Radiometric system.
Bacteria	:	***Mycobacterium tuberculosis $H_{37}Rv$***
Concentrtion	:	6.25 mg/ml.
Standard drug	:	Rifampin

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

[A] Synthesis of 1,N-Phenyl-3-β-pyridyl-4-formyl pyrazole

See part-I, Section -I(B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-one

To a well stirred solution of 1,N-Phenyl-3-β-pyridyl-4-formyl pyrazole (2.49 g, 0.01 M), p-Methylacetophenone (1.2 g, 0.01 M) in ethanol (25 ml) and 40% NaOH was added till the solution was basic. The reaction mixture was stirred for 24 hrs. The contents were poured on to crushed ice, acidified, filtered and crystallised from ethanol. Yield 75%; m.p. 128^{o}C.(Anal calcd. for $C_{24}H_{19}N_3O$ Found: C, 71.99; H, 4.68; N, 10.42; Required : C, 72.09; H, 4.54; N, 10.51%).

TLC solvent system : Acetone : Benzene (1: 9).

Similarly other substituted chalcones have been prepared. The physical data are recorded in Table No. 1.

[C] Antimicrobial activity of 1-Aryl-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-ones

All the products have been evaluated by antimicrobial activity as described under.

(a) Antimicrobial activity

It was carried out by cup-plate diffusion method which has been described as under.

(I) Antibacterial activity

The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of *B. cocous, B. subtillus, E. coli, P. vulgaris* in separate conical flasks at 40-50^{O}C and mixed well by gentle shaking. About 25 ml content of the flast were poured and evenly spread in a pertidish (13 cm in diameter) and allowed to set for 2 hrs. The cup (10 mm in diameter) were formed by the help of borar in agar medium and filled with 0.04 ml (40 mg) solution of sample in DMF.

The plates were incubated at 37^{O}C for 24 hrs. and the control was also maintained with 0.04 ml of DMF in a similar manner and the difference zones of inhibition of the bacterial growth with that of solvent were measured in millimeter and are recorded in graphical chart no.1.

(II) Antifungal activity

A. Niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on Sabouraud's agar slants. Sterilised Sabouraud's agar medium was inoculated with 72 hrs. old 0.5 ml of suspension of fungal spores in a separate flask. About 25 ml of the inculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm in diameter) were punched. The plates were incubated at 30^{O}C for 48 hrs. After the completion of incubation period, the zones of inhibition of growth in the form of diameter in mm was measured Along the test solution, in each petridish one cup was filled up with solvent which acts as control. The zones of inhibition are recorded in graphical chart no.1.

(b) Antitubercular Activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition and Co-ordinating Facility (TAACF), U.S.A. Primary screening of the compounds for antitubercular activity have been conducted at 6.25 mg/ml towards *Mycobacterium Tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the BACTEC 460 radiometric system. The compounds demonstrating atleast > 90%. inhibition in the primary screen have been retested at lower concentration towards *Mycobacterium Tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in the BACTEC 460.

The antitubercular activity data have been compared with standard drug Rifampin at 0.25 mg/ml concentration and it showed 98% inhibition. The data for % inhibition ware recorded in Table No. 1(a) onwards.

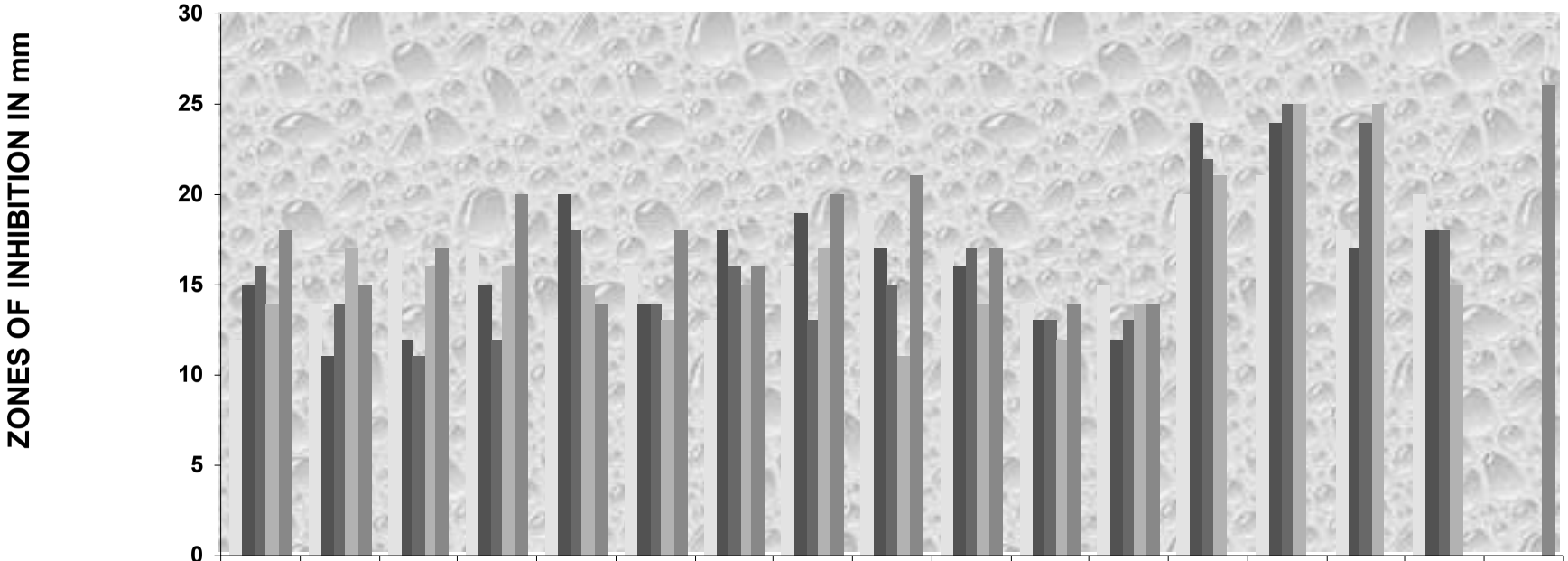
TABLE NO. 1 : PHYSICAL CONSTANTS OF 1-ARYL-3-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
1a	C_6H_5-	$C_{23}H_{17}N_3O$	351	140	0.61	81	11.96	11.79
1b	4-CH_3-C_6H_4-	$C_{24}H_{19}N_3O$	365	128	0.61	75	10.51	10.42
1c	4-OCH_3-C_6H_4-	$C_{24}H_{19}N_3O_2$	381	142	0.69	70	11.02	10.82
1d	2-OH-C_6H_4-	$C_{23}H_{17}N_3O_2$	367	118	0.57	82	11.44	11.25
1e	4-OH-C_6H_4-	$C_{23}H_{17}N_3O_2$	367	102	0.74	79	11.44	11.28
1f	4-Cl-C_6H_4-	$C_{23}H_{16}N_3OCl$	385.5	198	0.66	88	10.89	10.70
1g	4-F-C_6H_4-	$C_{23}H_{16}N_3OF$	369	162	0.64	79	11.38	11.21
1h	4-Br-C_6H_4-	$C_{23}H_{16}N_3OBr$	430	142	0.65	68	9.77	9.62
1i	3-NO_2-C_6H_4-	$C_{23}H_{16}N_4O_3$	396	248	0.51	89	14.13	14.01
1j	4-NO_2-C_6H_4-	$C_{23}H_{16}N_4O_3$	396	234	0.50	85	14.13	13.99
1k	4-NH_2-C_6H_4-	$C_{23}H_{18}N_4O$	366	181	0.71	74	15.29	15.11
1l	C_5H_4N-	$C_{22}H_{16}N_4O$	352	159	0.68	90	15.90	15.76

*TLC Solvent System : Acetone : Benzene

1 : 9

GRAPHICAL CHART NO.1 : PHYSICAL CONSTANTS OF 1-ARYL-3-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	12	14	17	17	13	16	13	16	19	17	14	15	20	21	18	20	0
B. subtillus	15	11	12	15	20	14	18	19	17	16	13	12	24	24	17	18	0
Ecoli	16	14	11	12	18	14	16	13	15	17	13	13	22	25	24	18	0
P. vulgaris	14	17	16	16	15	13	15	17	11	14	12	14	21	25	25	15	0
A. niger	18	15	17	20	14	18	16	20	21	17	14	14	0	0	0	0	26

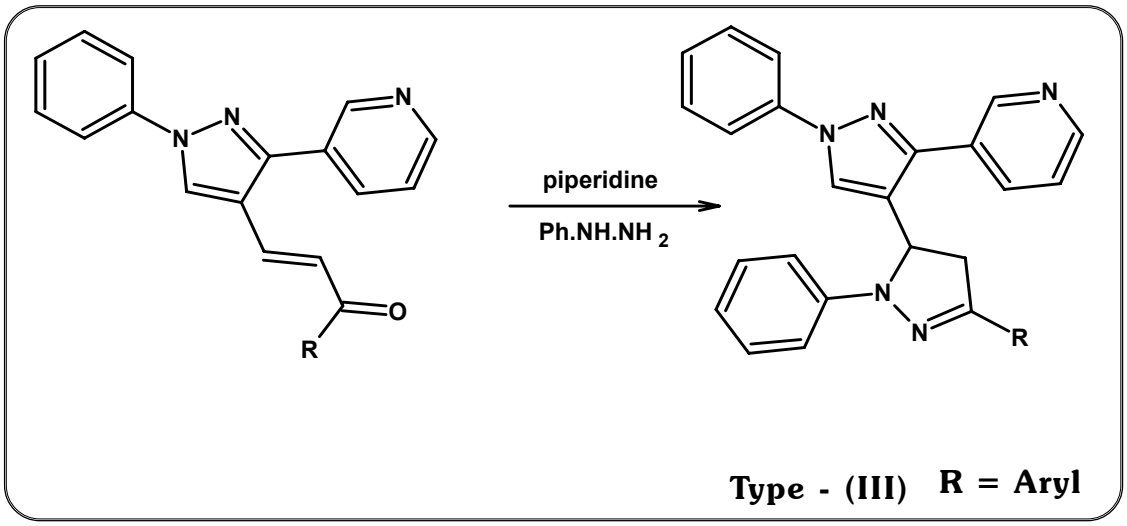
BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

	Antibacterial Activity zone of inhibition in mm			Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
1i(19)	1e(20)	1h(18)	1b(17)	1i(21)
1e(17)	1h(19)	1j(17)	1h(17)	1d(20)
1d(17)	1g(18)		1c(16)	1h(20)
1j(17)	1i(17)		1d(16)	
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

SECTION - III

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-PYRAZOLINES

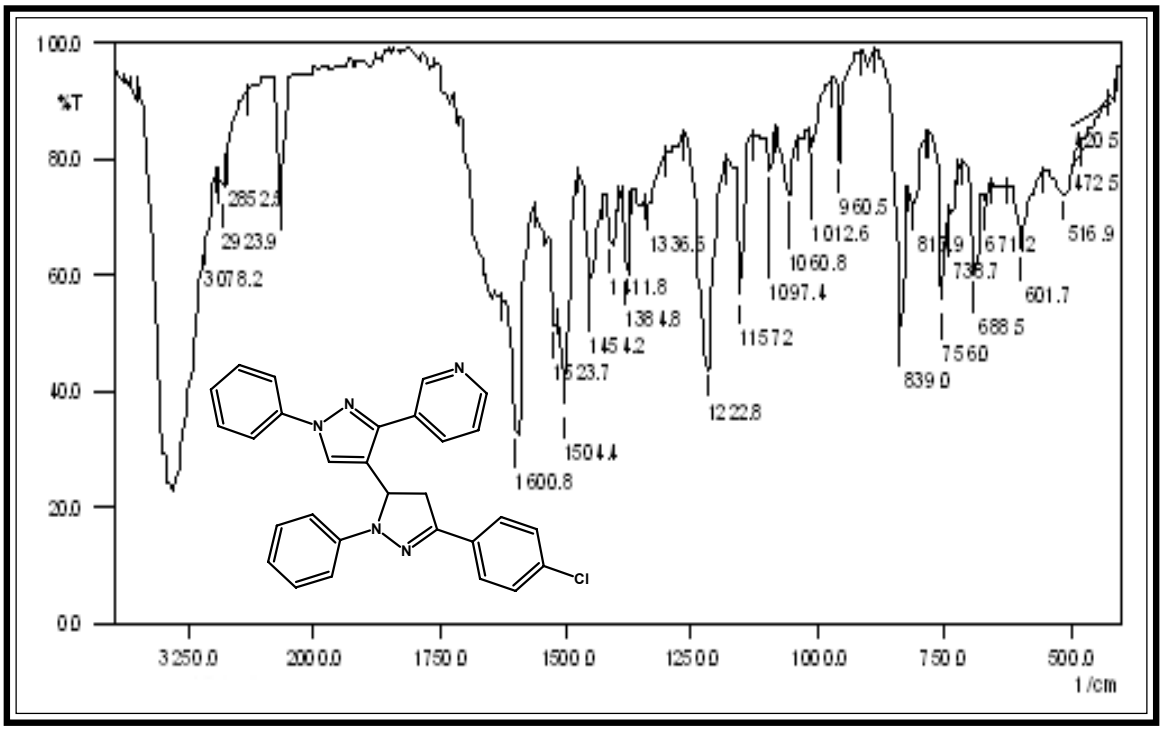
Looking to the interesting therapeutic activities of pyrazolines, it was considered worthwhile to synthesise compounds bearing 1,N-Phenyl-3-β-pyridyl-4-formyl pyrazole moiety linked to the pyrazoline of type- (III) which have been prepared by the action of 1-aryl-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-ones with phenyl hydrazine in presence of piperidine.



The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. The mass spectra of 1,N-Phenyl-3-(p-tolyl)-5-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-pyrazoline give m/z = 455 (recorded on Page No. 50). The fragmentation is also explained (Page No. 51).

The products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activities of synthesised compounds were compared with standard drugs.

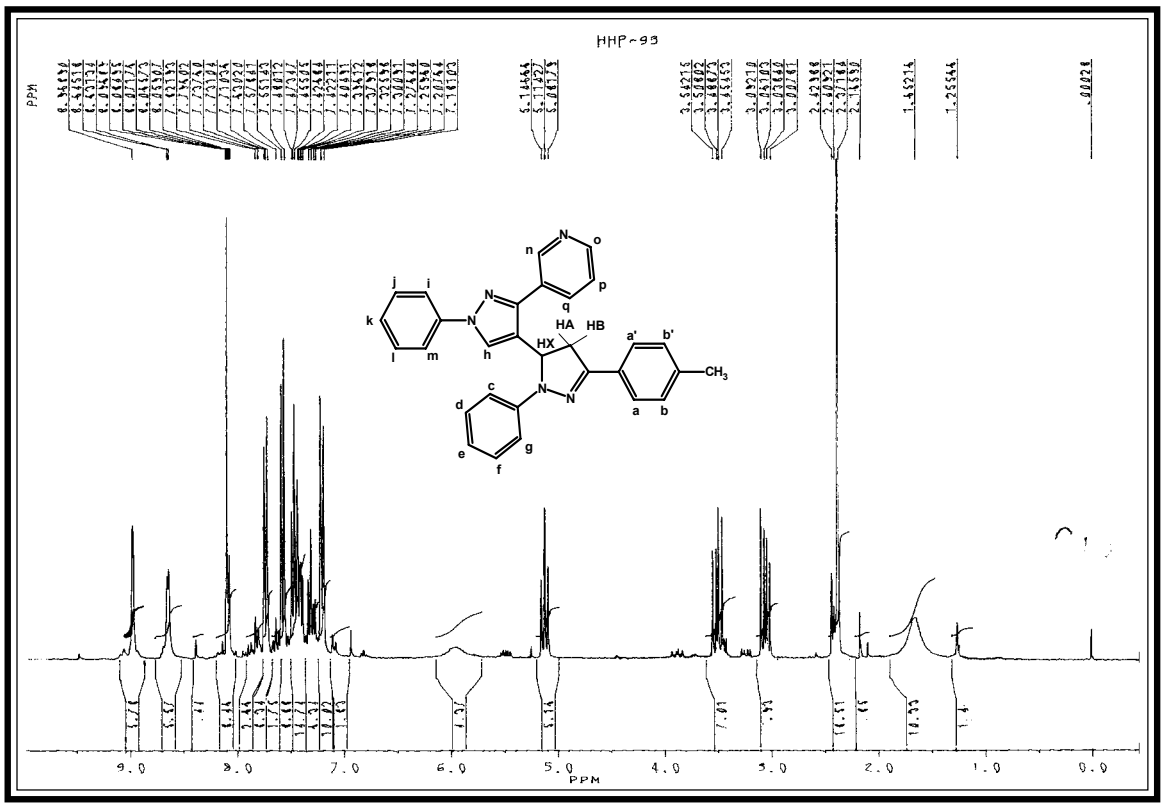
IR SPECTRAL STUDY OF 1,N-PHENYL-3-(p-CHLOROPHENYL)-5-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-PYRAZOLINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2920	95
$-CH_3$	C-H str. (sym.)	2852	2880-2850	,,
	C-H i.p.def. (asym.)	1411	1470-1435	,,
	C-H o.o.p. def. (sym.)	1384	1390-1370	,,
Aromatic	C-H str.	3078	3090-3030	96
	C=C str.	1502	1540-1480	,,
	C-H i.p. (def.)	1097	1125-1090	,,
	C-H o.o.p. (def)	839	835-810	,,
Pyrazole	C=N str.	1600	1610-1590	96
moiety	C-N str.	1222	1230-1020	,,
Pyrazoline	C-N str.	1097	1230-1020	,,
	C=N str.	1600	1650-1550	,,
Halide	C-Cl str.	756	600-800	95

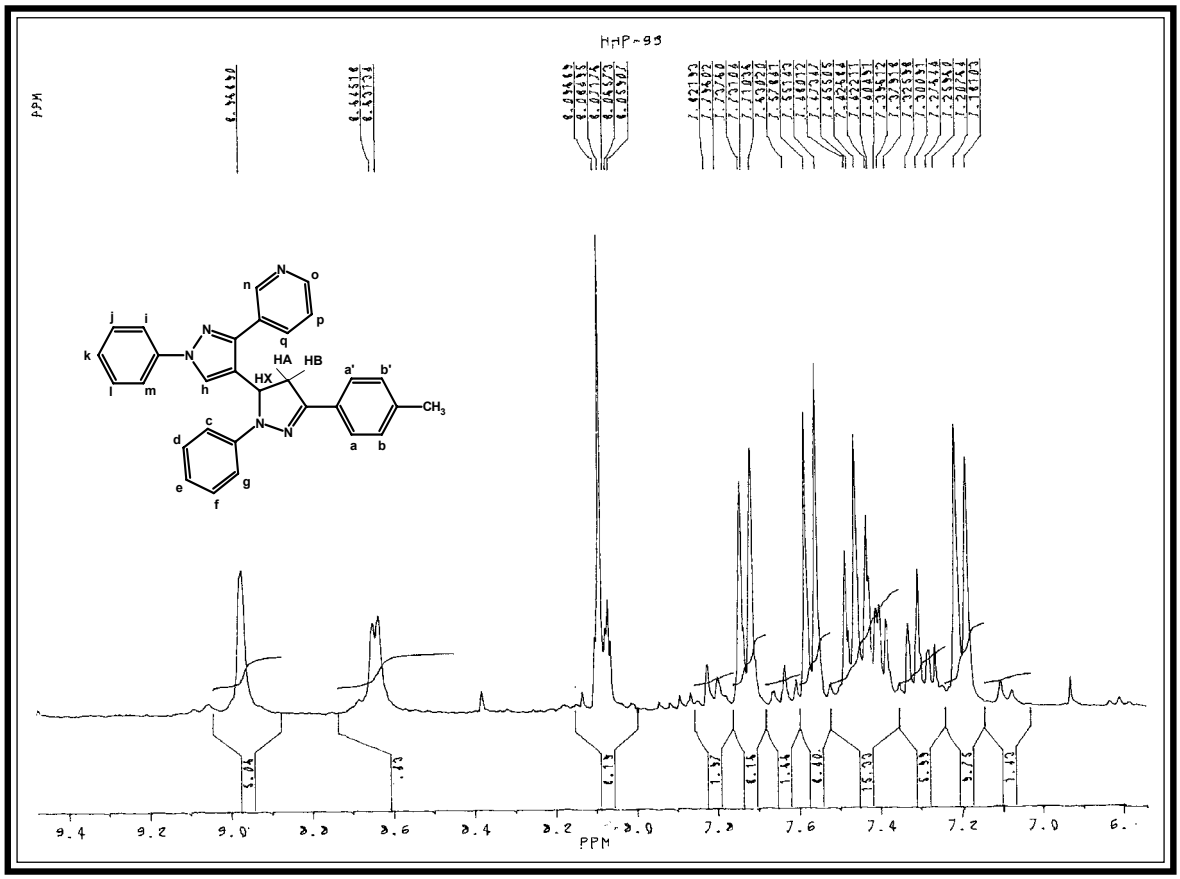
PMR SPECTRAL STUDY OF 1,N-PHENYL-3-(p-TOLYL)-5-[1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL]-PYRAZOLINE

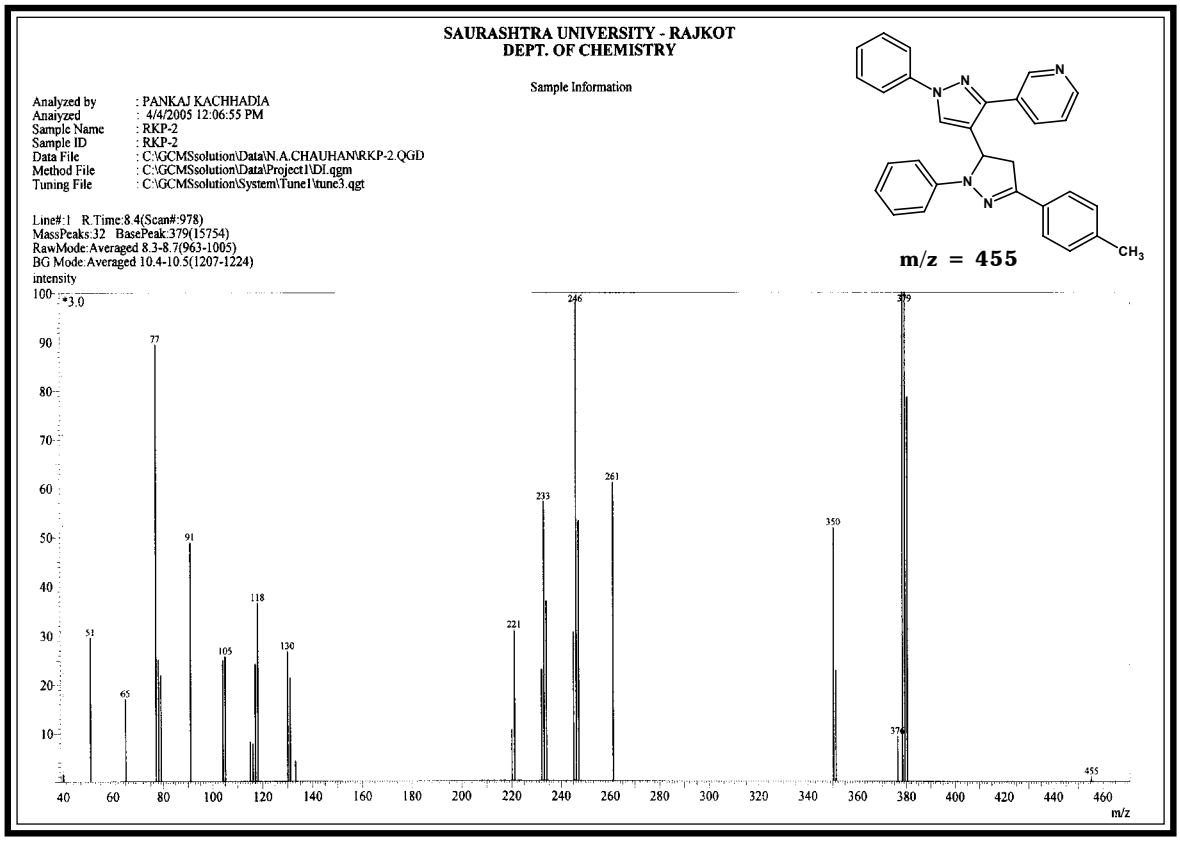


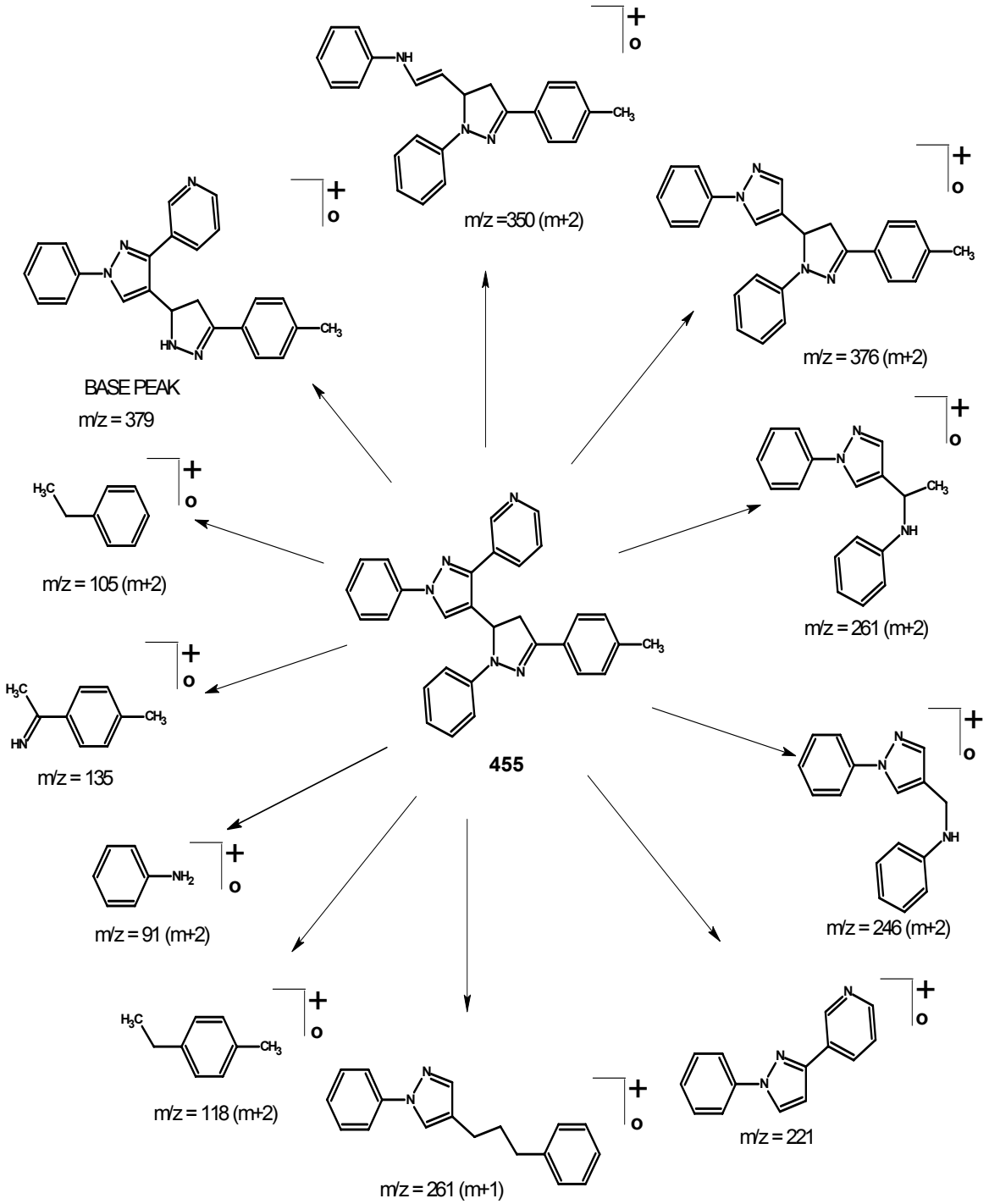
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.4	3H	singlet	Ar-CH3	-
2	3.00-3.09	1H	quartet	CHB	-
3	3.45-3.54	1H	quartet	CHA	-
4	5.08-5.18	1H	triplet	CHX	-
5	7.18-7.20	2H	doublet	Ar-CHa,a'	7.8
6	7.25-7.32	1H	doublet	Ar-CHp	7.5
7	7.42-7.48	3H	multiplet	Ar-CHf,d,q	-
8	7.55-7.57	4H	multiplet	Ar-CHj,l,g,c	-
9	7.63	1H	triplet	Ar-CHk	-
10	7.73-7.71	2H	doublet	Ar-CHb,b'	8.1
11	7.79-7.82	1H	triplet	Ar-CHe	-
12	8.05-8.09	3H	multiplet	Ar-CHi,m,o	-
13	8.61-8.63	1H	doublet	Ar-CHn	4.32
14	8.96	1H	singlet	Ar-CHh	-

EXPANDED AROMATIC REGION






m/z =350 (m+2)
m/z = 376 (m+2)
BASE PEAK
m/z = 379
m/z = 261 (m+2)
m/z = 105 (m+2)
m/z = 135
455
m/z = 246 (m+2)
m/z = 91 (m+2)
m/z = 118 (m+2)
m/z = 221
m/z = 261 (m+1)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-PYRAZOLINES

[A] Synthesis of 1,N-Phenyl-3-β-pyridyl-4-formyl pyrazole

See part-I, Section -I(B).

[B] Synthesis of 1-(p-Anisyl)-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-one

See Part-I, Section-II (B).

[C] Synthesis of 1,N-Phenyl-3-(p-anisyl)-5-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-pyrazoline

To a mixture of 1-(p-Anisyl)-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-2-propen-1-one (3.81 g, 0.01M) in 25 ml of absolute alcohol add phenyl hydrazine (1.08g, 0.01M) was added in the presence of basic catalyst like piperidine and refluxed for 12 hrs. at 70^{O}C. The reaction product was poured into ice. The product was isolated and crystallised from ethanol Yield 57%, m.p. 232^{O}C ($C_{30}H_{25}N_5O$; Found : C, 79.04%; H, 5.50%; N, 14.82%; Requires : C, 79.10%; H, 5.53%; N, 14.85%).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 2.

[D] Antimicrobial activity of 1,N-Phenyl-3-aryl-5-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'-yl)-pyrazolines

All the products have been evaluated by antimicrobial activity as described in Part-I, Section -II(C). The zone of inhibition of the test solutions are recorded in Chart No. 2.

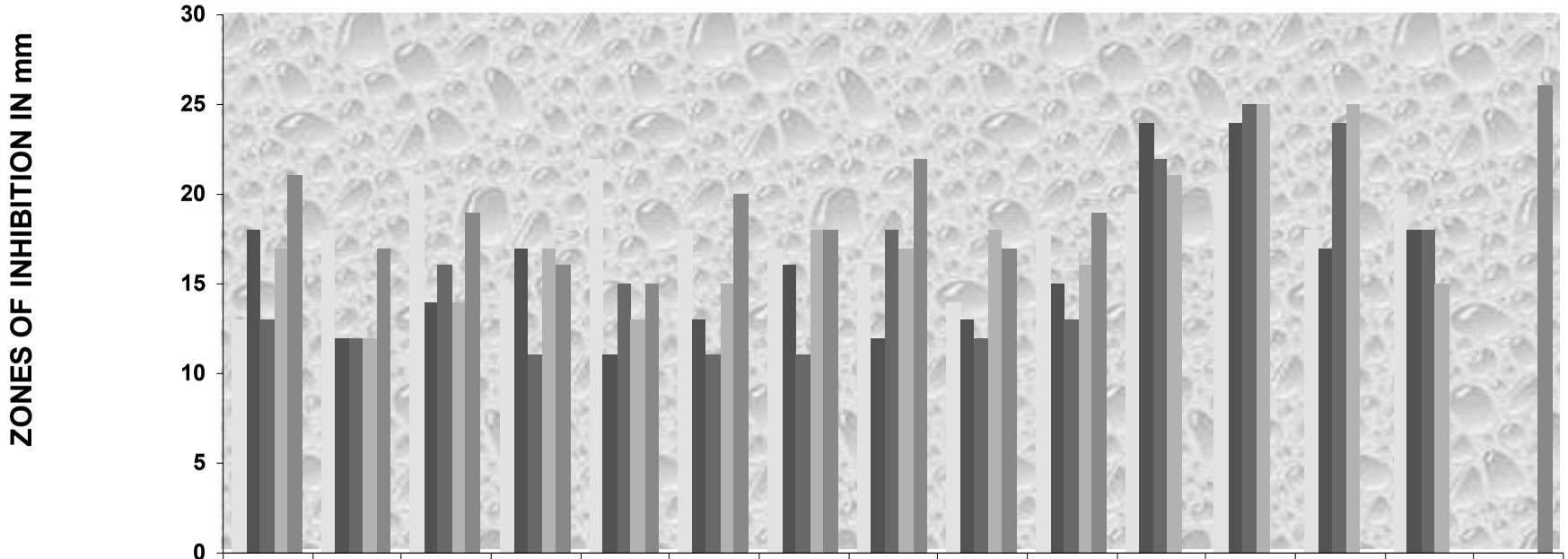
TABLE NO. 2 : PHYSICAL CONSTANTS OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-PYRAZOLINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
2a	4-CH_3-C_6H_4-	$C_{30}H_{25}N_5$	455	248	0.54	57	15.37	15.35
2b	4-OCH_3-C_6H_4-	$C_{30}H_{25}N_5O$	471	232	0.59	52	14.85	14.82
2c	2-OH-C_6H_4-	$C_{29}H_{23}N_5O$	457	186	0.48	60	15.31	15.28
2d	4-OH-C_6H_4-	$C_{29}H_{23}N_5O$	457	209	0.43	64	15.31	15.29
2e	4-Cl-C_6H_4-	$C_{29}H_{22}ClN_5$	475.5	172	0.55	67	14.71	14.68
2f	4-F-C_6H_4-	$C_{29}H_{22}FN_5$	459	224	0.39	58	15.24	15.21
2g	4-Br-C_6H_4-	$C_{29}H_{22}BrN_5$	520	256	0.33	49	13.46	13.43
2h	3-NO_2-C_6H_4-	$C_{29}H_{22}N_6O_2$	486	215	0.46	42	17.27	17.24
2i	4-NO_2-C_6H_4-	$C_{29}H_{22}N_6O_2$	486	230	0.38	50	17.27	17.26
2j	4-NH_2-C_6H_4-	$C_{29}H_{24}N_6$	456	197	0.52	55	18.41	18.40

*TLC Solvent System : Acetone : Benzene

3 : 7

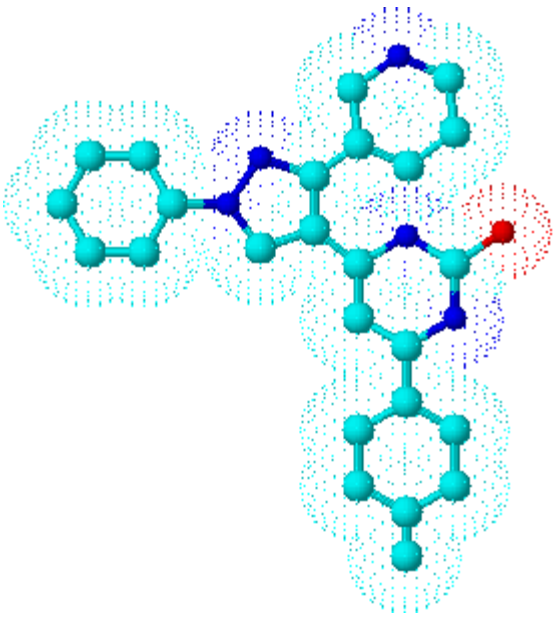
GRAPHICAL CHART NO. 2 : ANTIMICROBIAL ACTIVITY OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-PYRAZOLINESPYRAZOLINES



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	Amoxicillin	Benzoylpenic	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	13	18	21	15	22	18	17	16	14	18	20	21	18	20	0
B. subtillus	18	12	14	17	11	13	16	12	13	15	24	24	17	18	0
E.coli	13	12	16	11	15	11	11	18	12	13	22	25	24	18	0
P. vulgaris	17	12	14	17	13	15	18	17	18	16	21	25	25	15	0
A. niger	21	17	19	16	15	20	18	22	17	19	0	0	0	0	26

BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-β-PYRIDYL-PYRAZOL-4'-YL)-PYRAZOLINES

	Antibacterial Activity zone of inhibition in mm			Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
2e(22)	2a(18)	2h(18)	2g(18)	2h(22)
2c(21)	2d(17)	2c(16)	2i(18)	2a(21)
2b(18)		2d(17)	2f(20)	
2j(18)		2h(17)		
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

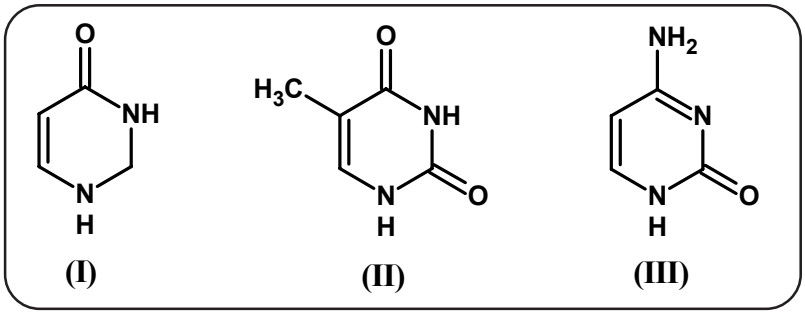


PART - II

STUDIES ON PYRIMIDINES

INTRODUCTION :-

Pyrimidine derivatives like uracil(I), thymine(II) and cytosin(III) occur widely in nature showing remarkable pharmaceutical importance because of their diverse biological activities. Several analoges of nucleic acids have been used as compounds that interfere with the synthesis and fuctioning of nucleic acids, an example is fluorouacil which has been used in the cancer treatment.

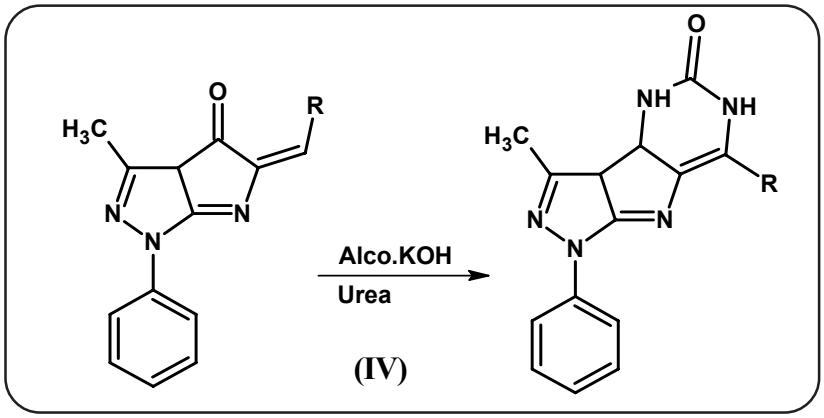


Pyrimdine ring carrying various substituents may be built up from two or three aliphatic fragments of other synthesis which are complimentary rather than alternative to it. Despite considerable localisation of π-electrons, at the nitrogen atom of oxopyrimidine and the sulphur atom of thiopyrimidine, the ring system is still sufficiently aromatic to possess substantial stability.

SYNTHETIC ASPECTS :-

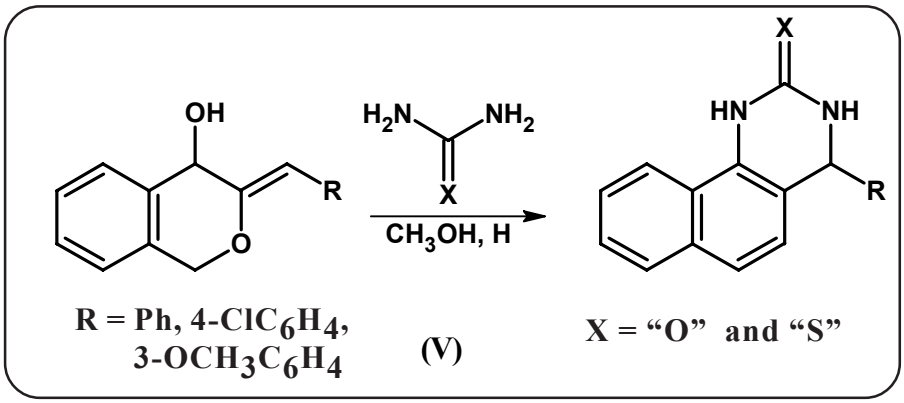
Popular methods for the preparation of pyrimidine derivatives have been reported by synthesis from a cyclic precursors, which have been described under the following synthesis.

1. Tauki Aaruki and co-workers [167] have prepared oxopyrimidine derivatives by treatment with urea in alcoholic KOH.
2. Hussain Ali Saleiman et. al.[168] have prepared oxoyrimidine derivatives(IV) by using urea in alcoholic KOH.



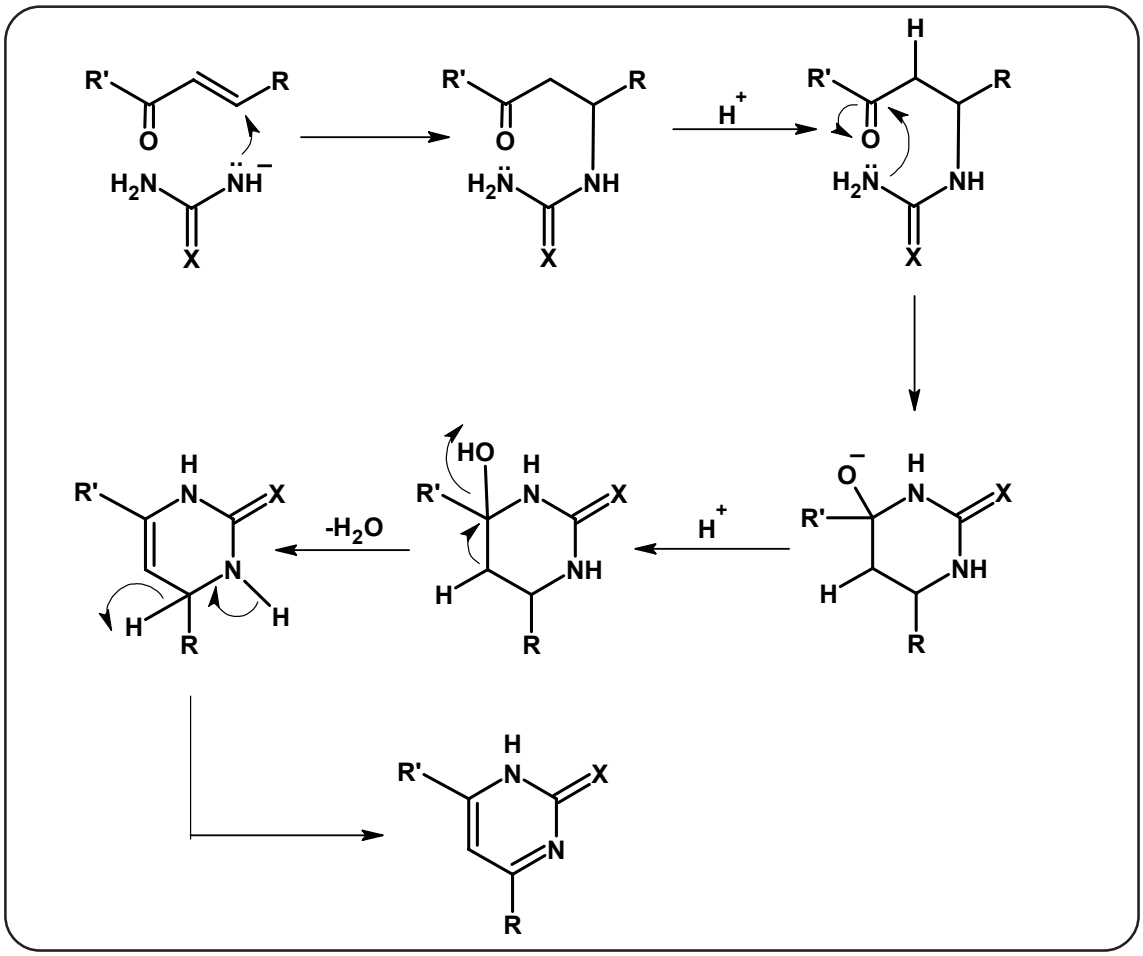
3. By the condensation of â-keto ester with thiourea and aldehyde[169-170].

4. Wang Jinjum[171] have prepared some new benzo[c] pyrano[4,3-d] pyrimidine derivatives(V).



MECHANISM :

The reaction proceeds through conjugated addition of thiourea or urea to the α,β-unsaturated system. The bond formation take place between N-atom of thiourea or urea and C-atom of chalcone.



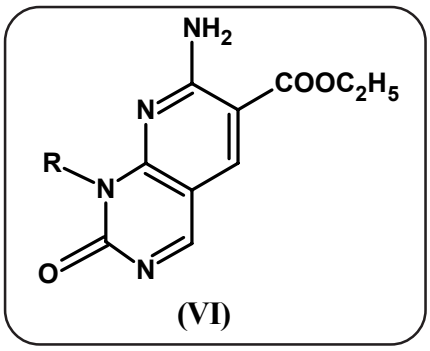
In the first step migration of electron takes place due to the more electronegativity of O-atom than C-atom. So carbon has positive charge while nitrogen atom looses proton so it aquires negative charge, with simultaneous removal of water.

THERAPEUTIC IMPORTANCE

Pyrimidine derivatives have proven to be of great importance in exhibiting and enhancing the bilogical activities as shown under.

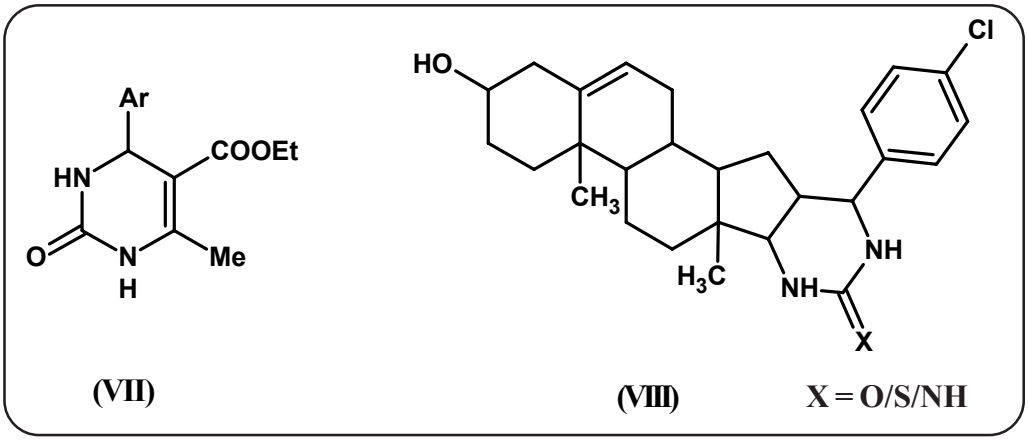
1. Antimalarial[172]
2. Antithyroid[173]
3. Anticancer[174]
4. Antiinflammatory and analgesic[175-177]
5. Antineoplastic[178,179]
6. Antiviral and antitumor[180,181]
7. Anti AIDS[182]
8. Antimicrobial[183]
9. Anticytotoxic[184]
10. Herbicidal[185,86]

J. Lewis[187] have prepared oxo-pyrimidines and found to be active as bactericidal and antiviral, H. Junek and co-workers[188] have prepared pyrimidines (VI) which were found to possess antiviral activity.



(VI)

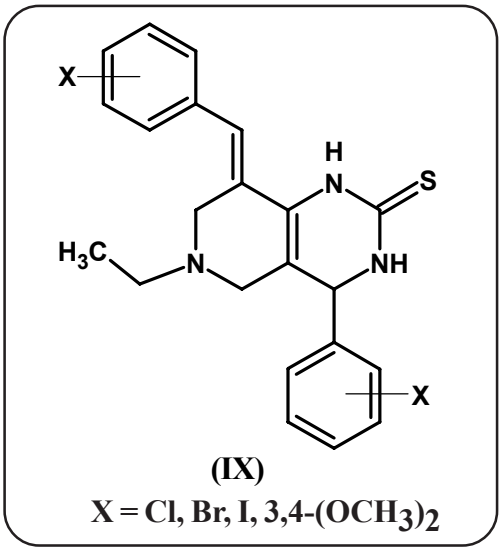
Baldev Kumar et. al.[189] have prepared some new oxopyrimidine derivatives (VII) and reported them as potent calcium channel blockers. Abd. EL-Galil and M. Abdulla[190] have synthesised some fused steroidal oxopyrimidine derivatives (VIII) and reported them as androgenic anabolic agent as well as antiinflammatory agent.



(VII) **(VIII)** **X = O/S/NH**

Erker T. et. al.[191] have prepared thiopyrimidines which have been shown to possess muscle relaxant activity. Breozowskii Z. [192] found thiopyrimidine as anti-HIV. Nakatsuka M. et. al. [193] prepared thiopyrimidines active against inflammmation.

Abou EL-Fotooh et. al.[194] prepared thiopyrimidine derivatives (IX) which showed anticancer activity.



(IX)

X = Cl, Br, I, 3,4-$(OCH_3)_2$

Pyrimidine derivatives have attracted us in view of their great biological activity. Taking this into considertion, the synthesis of some novel pyrimidines has been designed which are described as under.

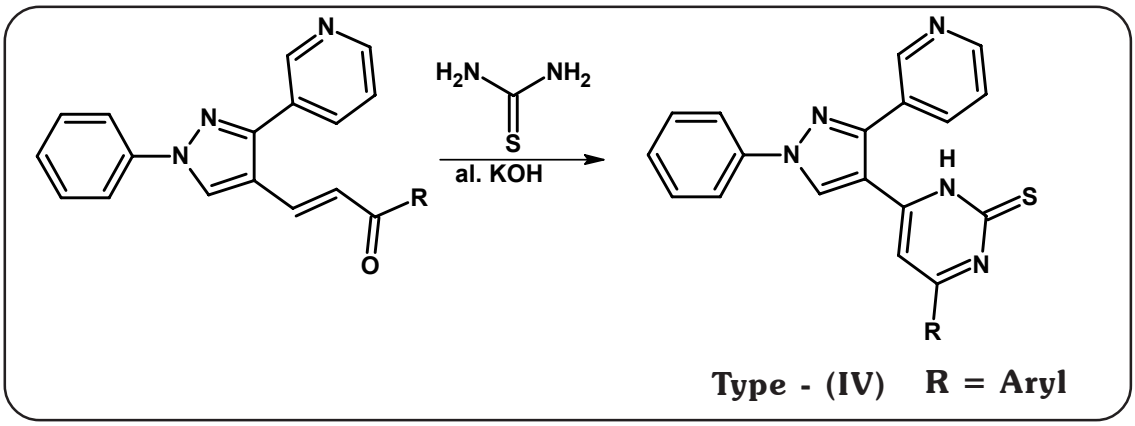
SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONES

SECTION - II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONES

With a view to synthesising the compounds having better therapeutic activity the pyrimidines of type (IV) have been prepared by the condensation of 1-Aryl-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one and thiourea in presence of al. KOH as catalyst as given below.



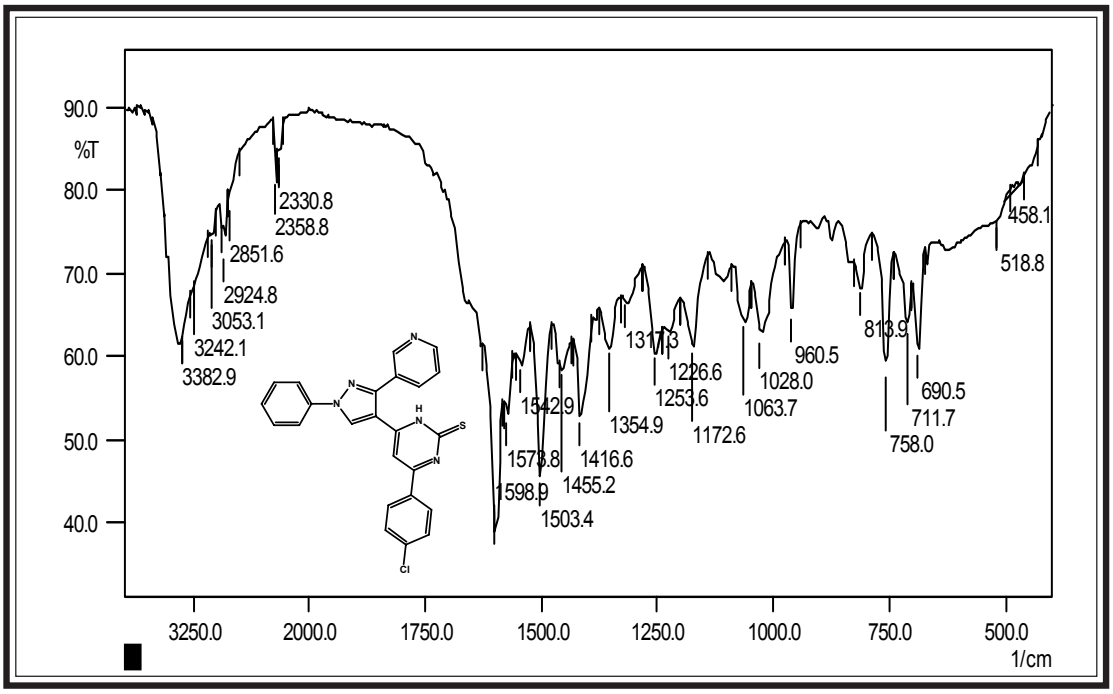
Type - (IV) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy. The mass spectra of 6-(p-Tolyl)-4-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-thione give m/z = 421 (recorded on Page No. 64). The fragmentation is also explained (Page No. 65).

All the products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs.

The synthesised compounds have been screened for their *in vitro* biological assay like antitubercular activity towards a strain of *Mycobacterium tuberculosis* $H_{37}Rv$ at concentration of 6.25 mg/ml using Rifampin as standard drug.

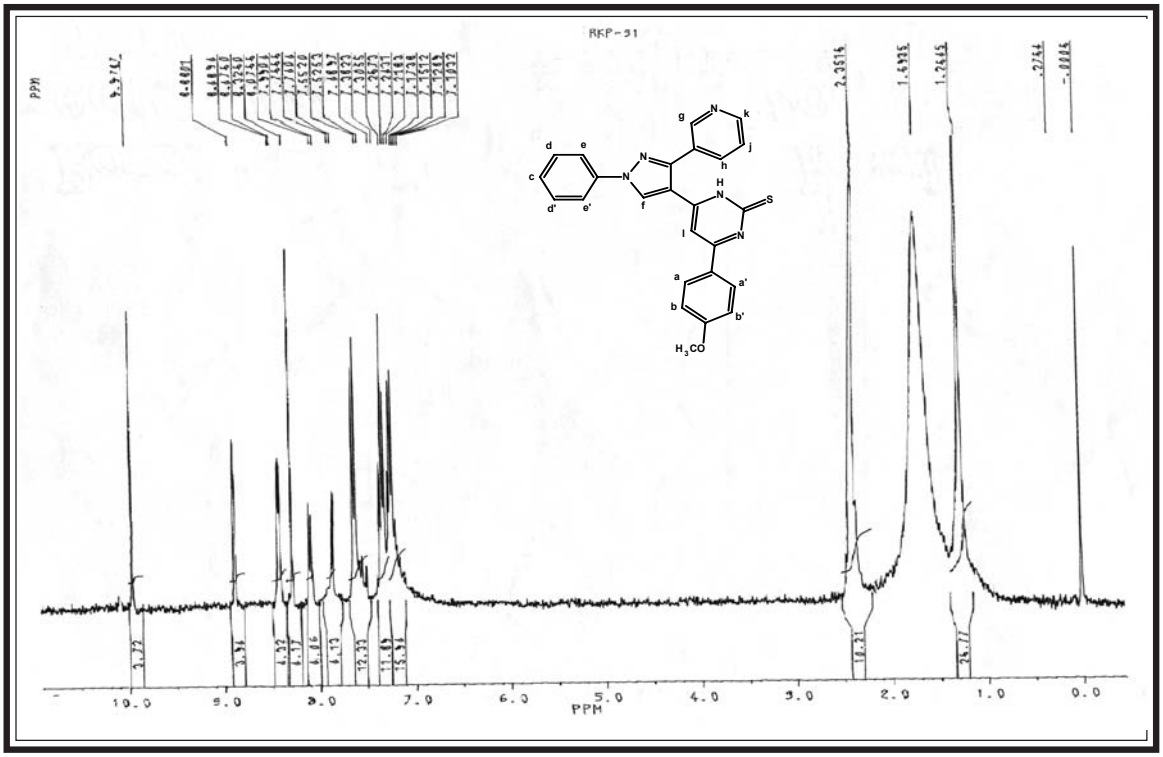
IR SPECTRAL STUDY OF 6-(p-CHLOROPHENYL)-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2924	2975-2920	95
-CH_3	C-H str. (sym.)	2851	2880-2850	,,
	C-H i.p.def. (asym.)	1446	1470-1435	,,
	C-H o.o.p. def. (sym.)	1354	1390-1370	,,
Aromatic	C-H str.	3053	3090-3030	96
	C=C str.	1598	1540-1480	,,
	C-H i.p. (def.)	1172	1125-1090	,,
	C-H o.o.p. (def)	813	835-810	,,
Pyrazole	C=N str.	1573	1610-1590	95
moiety	C-N str.	1226	1230-1020	,,
Thio				
pyrimidine	C-N str.	1226	1230-1020	,,
	N-H str.	3382	3400-3250	,,
	C=S str.	1172	1200-1020	,,
Halide	C-Cl str.	758	600-800	96

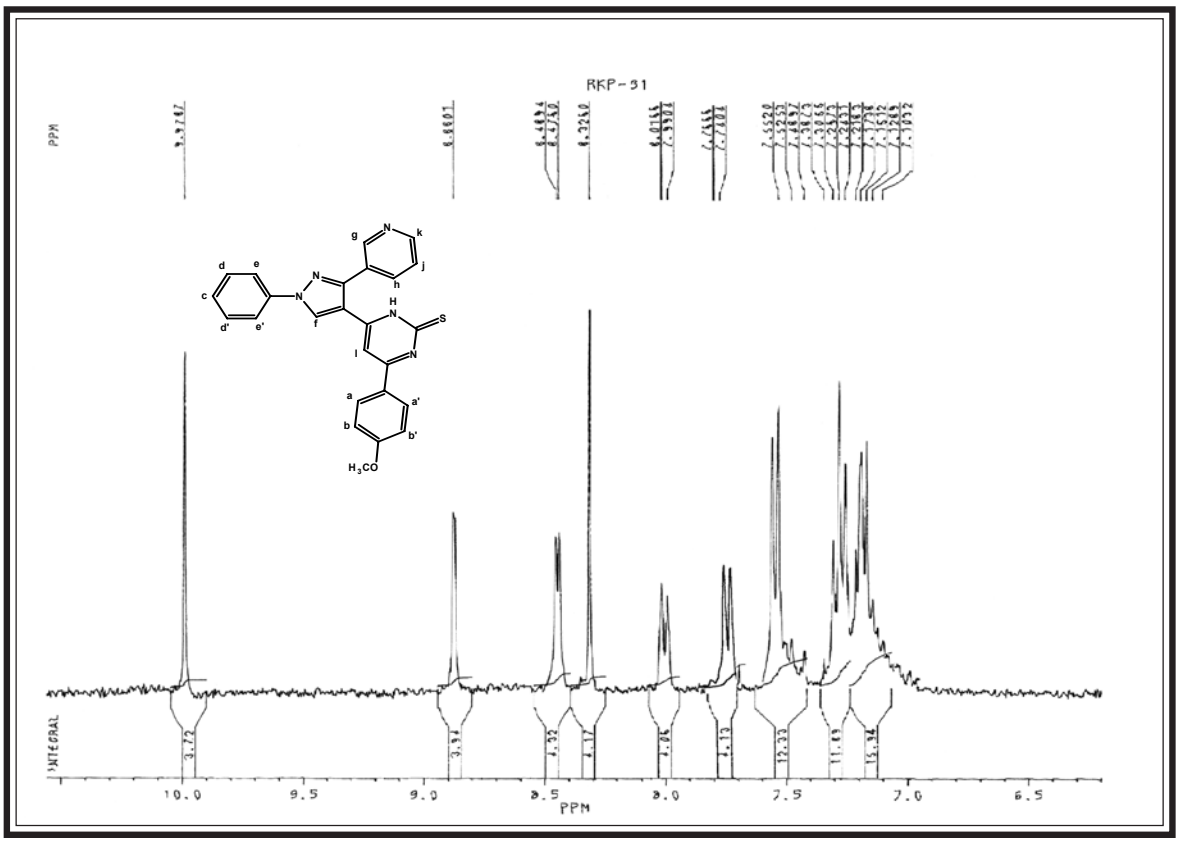
PMR SPECTRAL STUDY OF 6-(p-ANISYL)-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONE



Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.35	3H	singlet	Ar-CH_3	-
2	7.10-7.17	4H	multiplet	Ar-Ha,a'	-
				Ar-Hb,b'	-
3	7.24-7.30	3H	multiplet	Ar-Hc,dd'	-
4	7.48-7.55	3H	multiplet	Ar-Hl,ee'	-
5	7.74-7.77	1H	doublet	Ar-Hh	7.86
6	7.99-8.01	1H	doublet	Ar-Hj	7.84
7	8.32	1H	singlet	Ar-Hf	-
8	8.47-8.48	1H	doublet	Ar-Hk	-
9	8.88	1H	singlet	Ar-Hg	-
10	9.97	1H	singlet	-NH	-

EXPANDED AROMATIC REGION

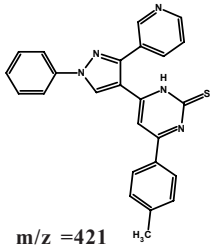


SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

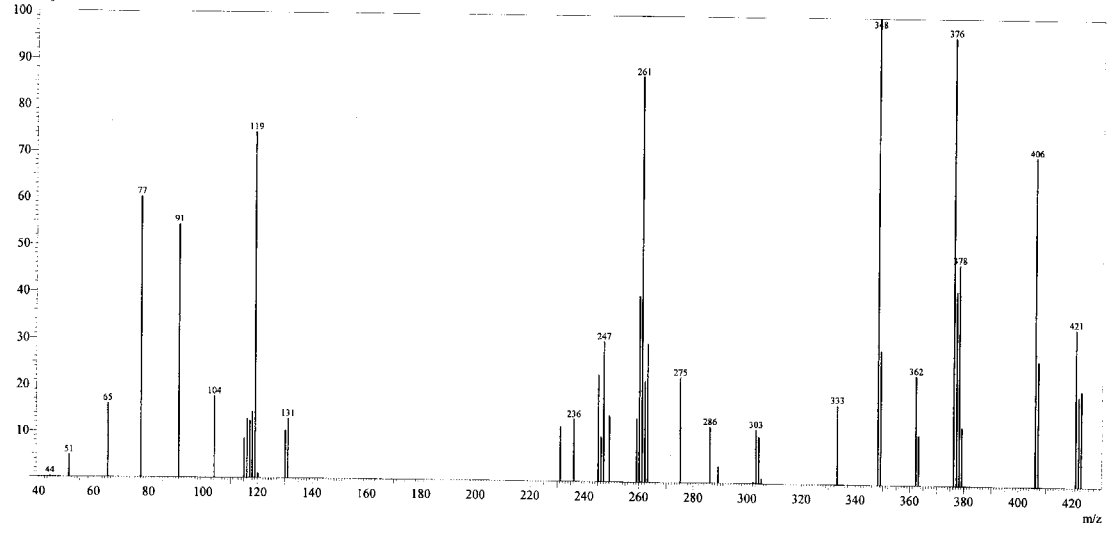
Sample Information

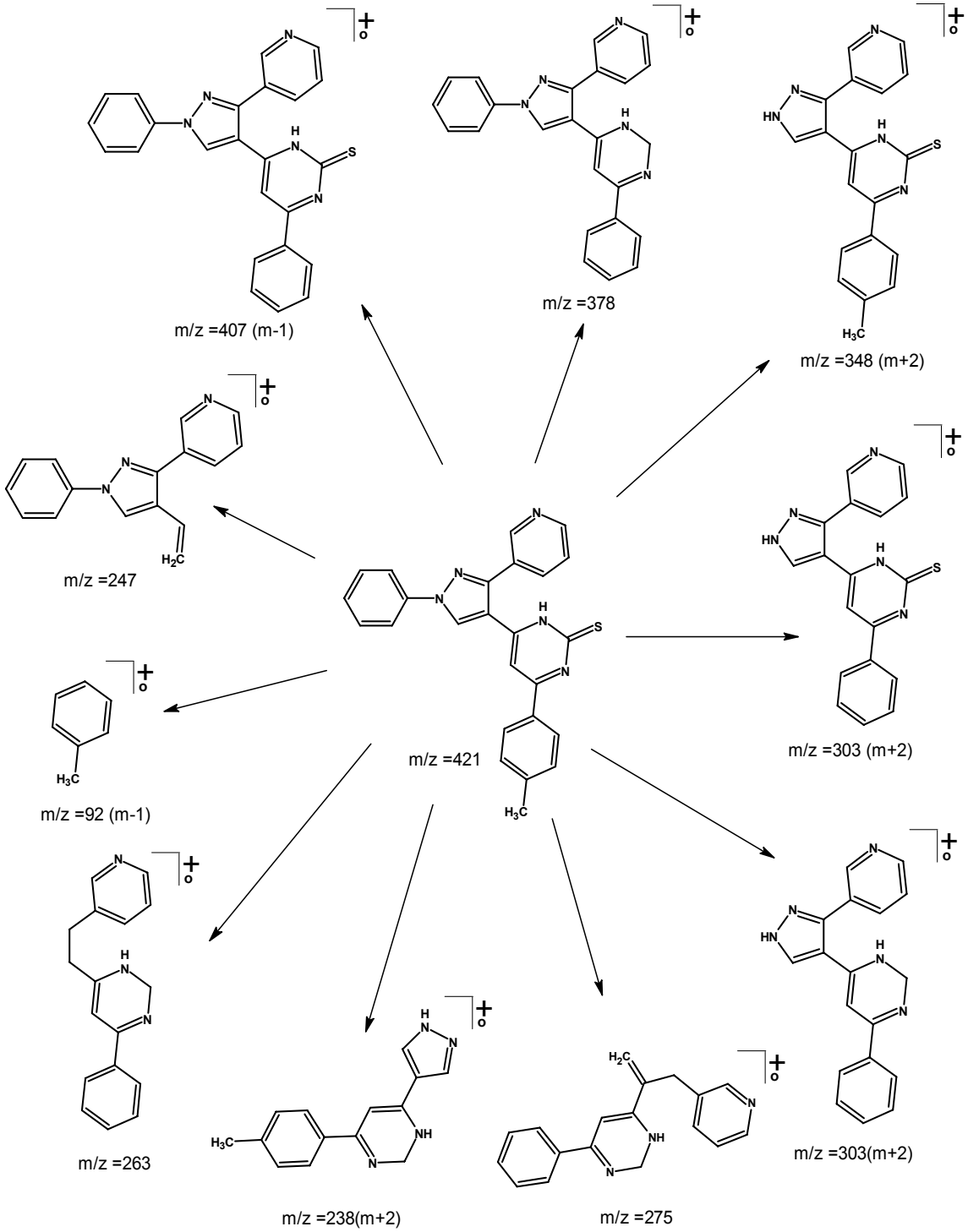
Analyzed by : PANKAJ KACHHADIA
Analyzed : 7/4/2005 1:11:19 PM
Sample Name : RKP-16
Sample ID : RKP-16
Data File : C:\GCMSsolution\Data\N.A.CHAUHAN\RKP-16.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune8.qgt

Line#:1 R.Time:6.9(Scan#:797)
MassPeaks:46 BasePeak:348(9476)
RawMode:Averaged 6.8-7.1(782-815)
BG Mode:Averaged 3.0-3.3(324-356)



m/z =421




m/z =407 (m-1)
m/z =378
m/z =348 (m+2)
m/z =247
m/z =303 (m+2)
m/z =421
m/z =92 (m-1)
m/z =263
m/z =303(m+2)
m/z =238(m+2)
m/z =275

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONES

[A] Synthesis of 1-Phenyl-3-â-pyridyl-4-formyl pyrazole

See part-I, Section -I(B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one

See Part-I, Section-II (B).

[C] Synthesis of 6-(p-Tolyl)-4-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-thione

To a mixture of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one (3.65 g, 0.01M) in 25 ml of absolute alcohol add al. KOH and refluxed for 12 hrs. at 70^{o}C. The reaction product was poured into ice. The product was isolated and crystallised from ethanol Yield 54%, m.p. 232^{o}C ($C_{25}H_{21}N_5S$; Found : C, 71.14%; H, 4.52%; N, 16.59%; Requires :C, 71.23%; H, 4.54%; N, 16.61%;).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 3.

[D] Antimicrobial activity of 6-Aryl-4-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-thiones

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solutions are recorded in Graphical Chart No.3.

Antitubercular screening of the compounds of type(IV) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-II (C) and the percentage of inhibition data of the compounds are recorded in Table No. 3a.

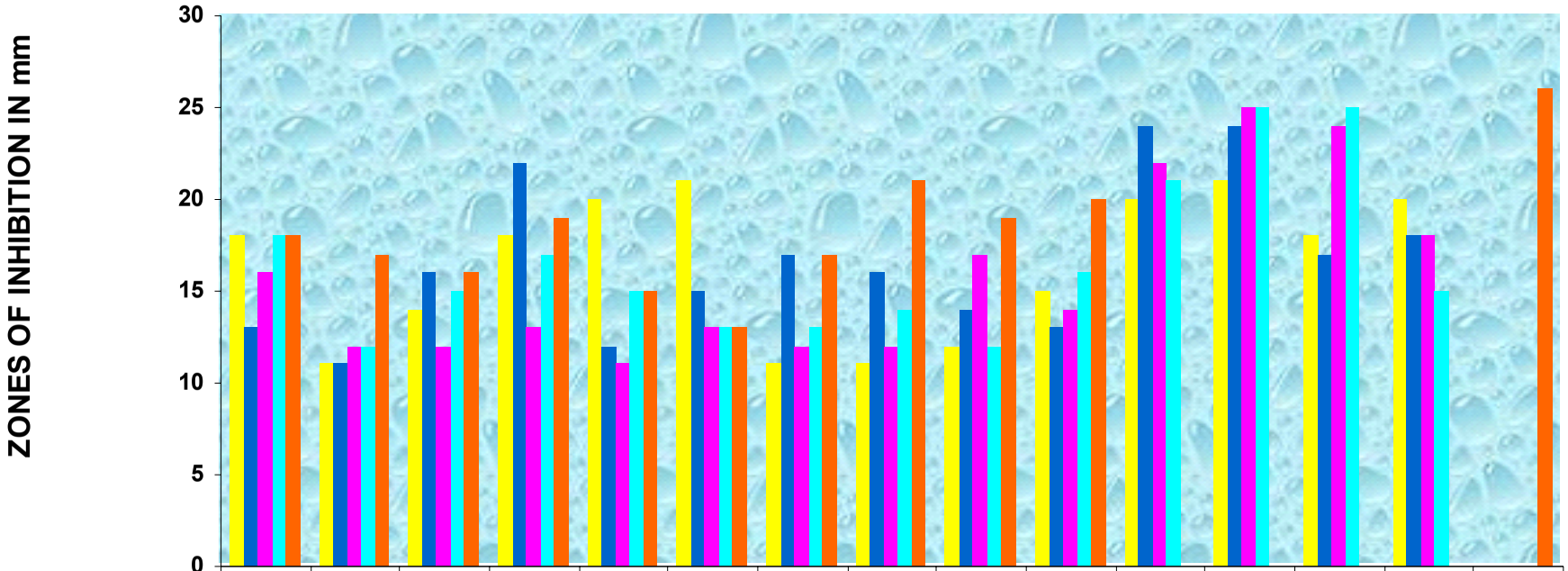
TABLE NO. 3 : PHYSICAL CONSTANTS OF PHYSICAL CONSTANTS OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. ^{o}C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
3a	4-CH_3-C_6H_4-	$C_{25}H_{19}N_5S$	421	232	0.42	54	16.61	16.59
3b	4-OCH_3-C_6H_4-	$C_{25}H_{19}N_5OS$	437	255	0.48	50	16.01	15.97
3c	2-OH-C_6H_4-	$C_{24}H_{17}N_5OS$	423	208	0.47	47	16.54	16.52
3d	4-OH-C_6H_4-	$C_{24}H_{17}N_5OS$	423	223	0.52	53	16.54	16.52
3e	4-Cl-C_6H_4-	$C_{24}H_{16}ClN_5S$	441.5	195	0.49	62	15.85	15.82
3f	4-F-C_6H_4-	$C_{24}H_{16}FN_5S$	425	240	0.38	55	16.46	16.44
3g	4-Br-C_6H_4-	$C_{24}H_{16}BrN_5S$	486	259	0.50	51	14.40	14.37
3h	3-NO_2-C_6H_4-	$C_{24}H_{16}N_6O_2S$	452	276	0.42	49	18.57	18.54
3i	4-NO_2-C_6H_4-	$C_{24}H_{16}N_6O_2S$	452	210	0.51	60	18.57	18.56
3j	4-NH_2-C_6H_4-	$C_{24}H_{18}N_6S$	422	212	0.57	48	19.89	19.87

*TLC Solvent System : Acetone : Benzene

3 : 7

GRAPHICAL CHART NO. 3 ; ANTIMICROBIAL ACTIVITY OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONES

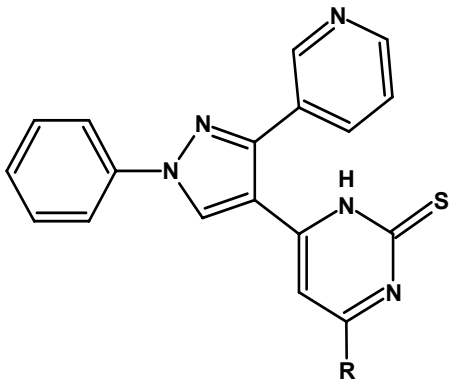


	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	Amoxicillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	18	11	14	18	20	21	11	11	12	15	20	21	18	20	0
B. subtillus	13	11	16	22	12	15	17	16	14	13	24	24	17	18	0
Ecoli	16	12	12	13	11	13	12	12	17	14	22	25	24	18	0
P. vulgaris	18	12	15	17	15	13	13	14	12	16	21	25	25	15	0
A. niger	18	17	16	19	15	13	17	21	19	20	0	0	0	0	26

BIOLOGICAL EVALUTION OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-THIONES

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	*B. subtillus*	*E. coli*	*P. vulgaris*	*A. niger*
1	2	3	4	5
3f(21)	3d(22)	3i(17)	3g(18)	3h(22)
3e(20)	3g(17)	3a(16)	3d(17)	3j(20)
3a(18)	3c(16)	3j(16)	3d(19)	
3d(18)	3h(16)	3e(15)	3h(18)	
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

TABLE NO. 3a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

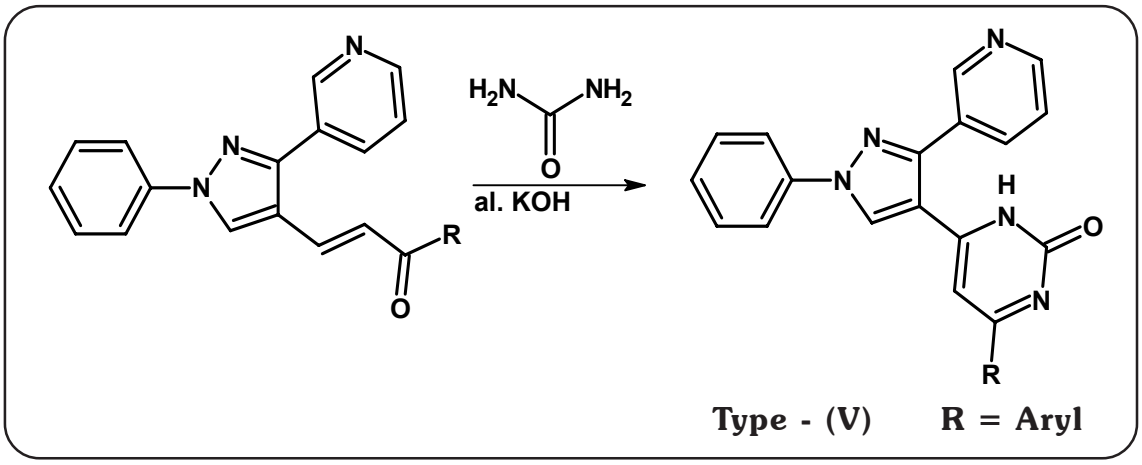
Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC mg/ml*	*% Inhib*	*Activity*	*Comment*
RKP-65	295733	4-NH_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	35	-	MIC Rifampin =
RKP-66	295734	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	26	-	0.25 mg/ml
RKP-67	295735	4-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	20	-	@ 98% Inhibition
RKP-68	295736	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	02	-	"
RKP-69	295737	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-70	295738	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	33	-	"
RKP-71	295739	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	30	-	"
RKP-72	295740	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	16	-	"
RKP-73	295741	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	9	-	"
RKP-74	295742	4-CH_3-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	15	-	"

SECTION - II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONES

With a view to synthesising the compounds having better therapeutic activity the pyrimidines of type (V) have been prepared by the condensation of 1-Aryl-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-ones and urea in presence of al. KOH as catalyst as given below.

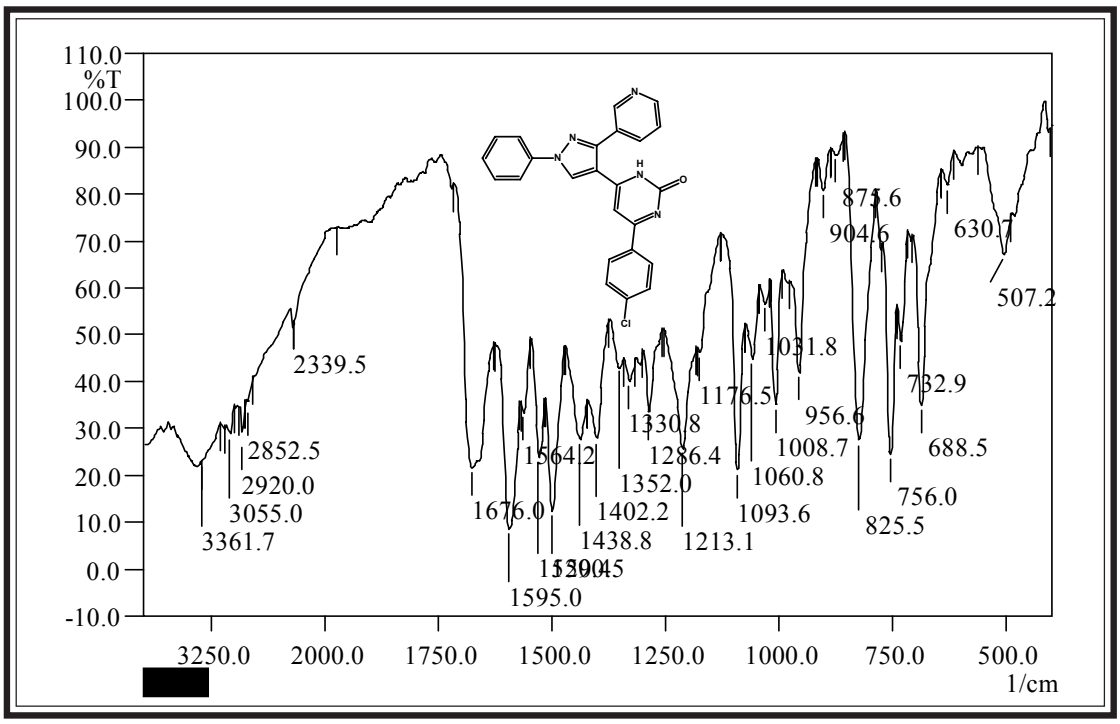


The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy. The mass spectra of 6-(p-Tolyl)-4-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-one give m/z = 407 (recorded on Page No. 74). The fragmentation is also explained (Page No. 75).

All the products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs.

The synthesised compounds have been screened for their *in vitro* biological assay like antitubercular activity towards a strain of *Mycobacterium tuberculosis* $H_{37}Rv$ at concentration of 6.25 mg/ml using Rifampin as standard drug.

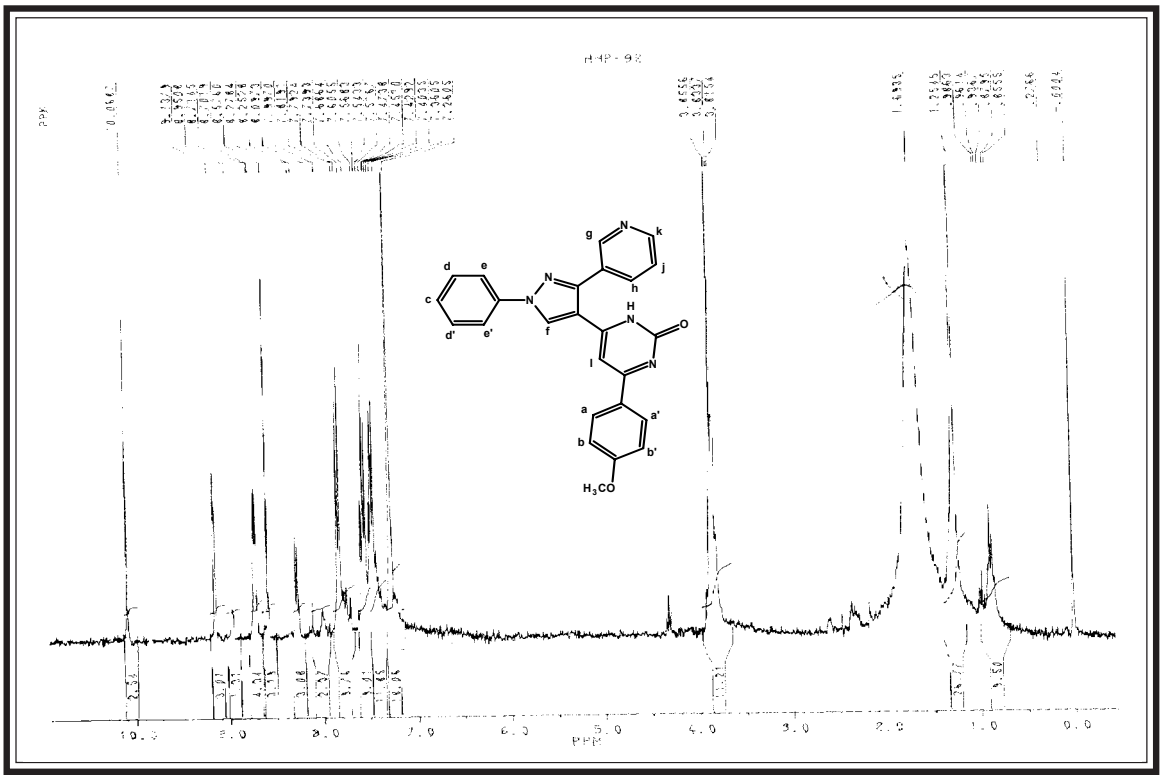
IR SPECTRAL STUDY OF 6-(p-CHLOROPHENYL)-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONE



Instrument : **SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)**

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2920	2975-2920	95
-CH_3	C-H str. (sym.)	2852	2880-2850	,,
	C-H i.p.def. (asym.)	1438	1470-1435	,,
	C-H o.o.p. def. (sym.)	1352	1390-1370	,,
Aromatic	C-H str.	3055	3090-3030	96
	C=C str.	1595	1540-1480	,,
	C-H i.p. (def.)	1093	1125-1090	,,
	C-H o.o.p. (def)	825	835-810	,,
Pyrazole	C=N str.	1595	1610-1590	95
moiety	C-N str.	1213	1230-1020	,,
Oxo pyrimidine	C-N str.	1213	1220-1020	,,
	N-H str.	3361	3400-3250	,,
	C=Ostr.	1676	1700-1640	,,
Halide	C-Cl str.	750	600-800	96

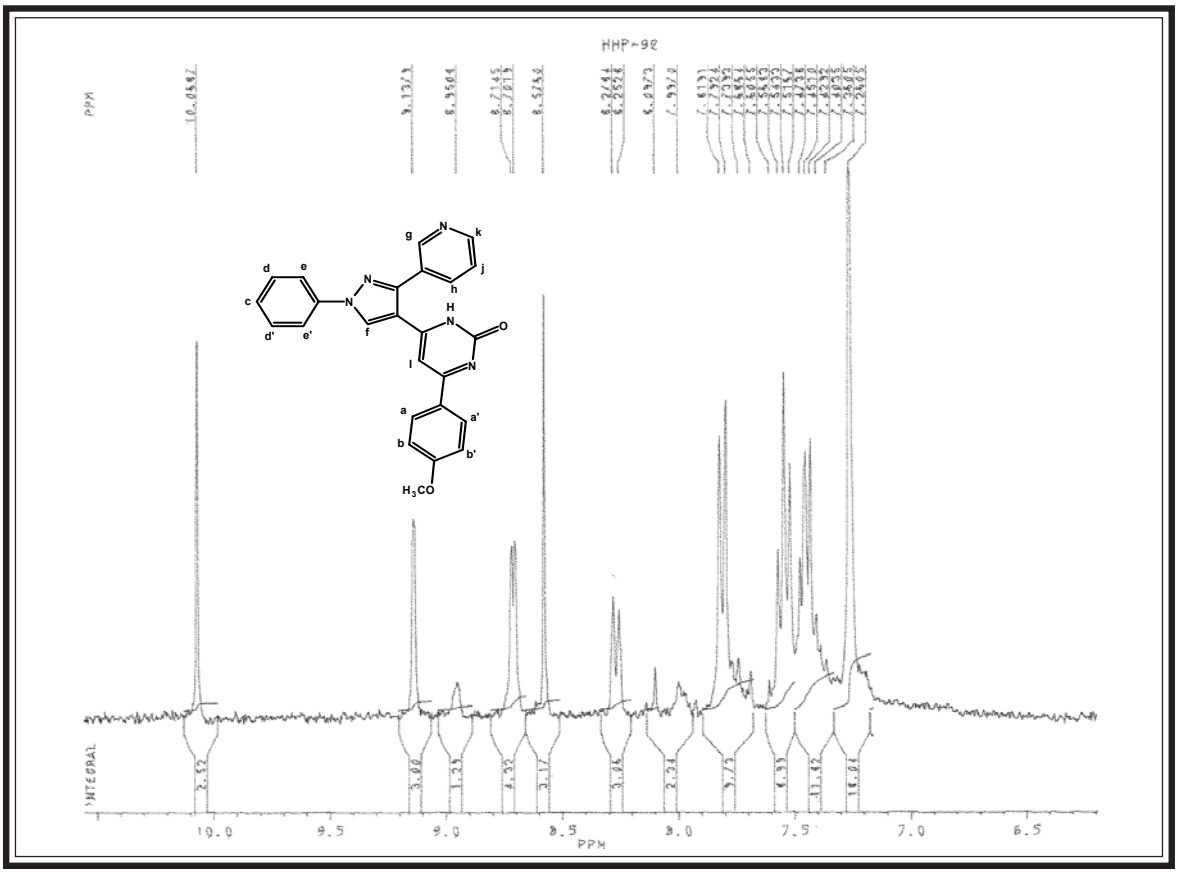
PMR SPECTRAL STUDY OF 6-(p-ANISYL)-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONE

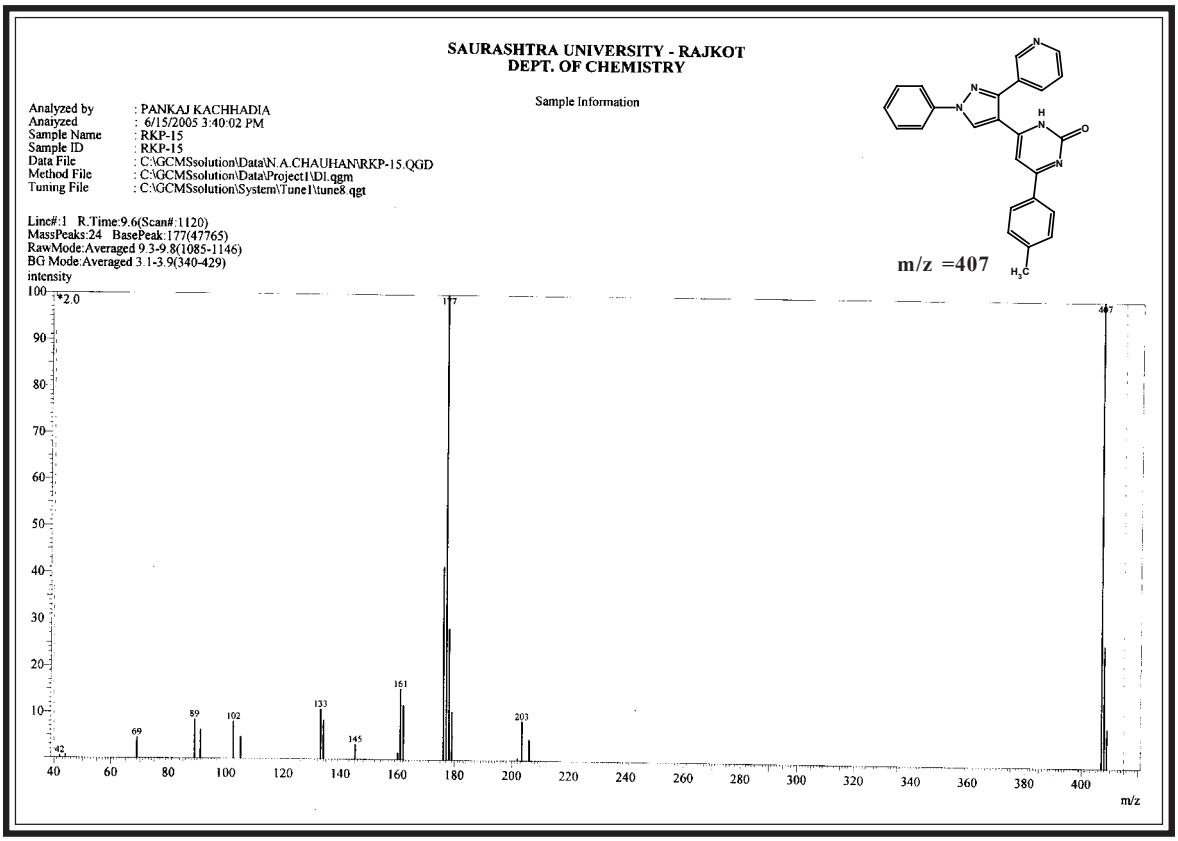


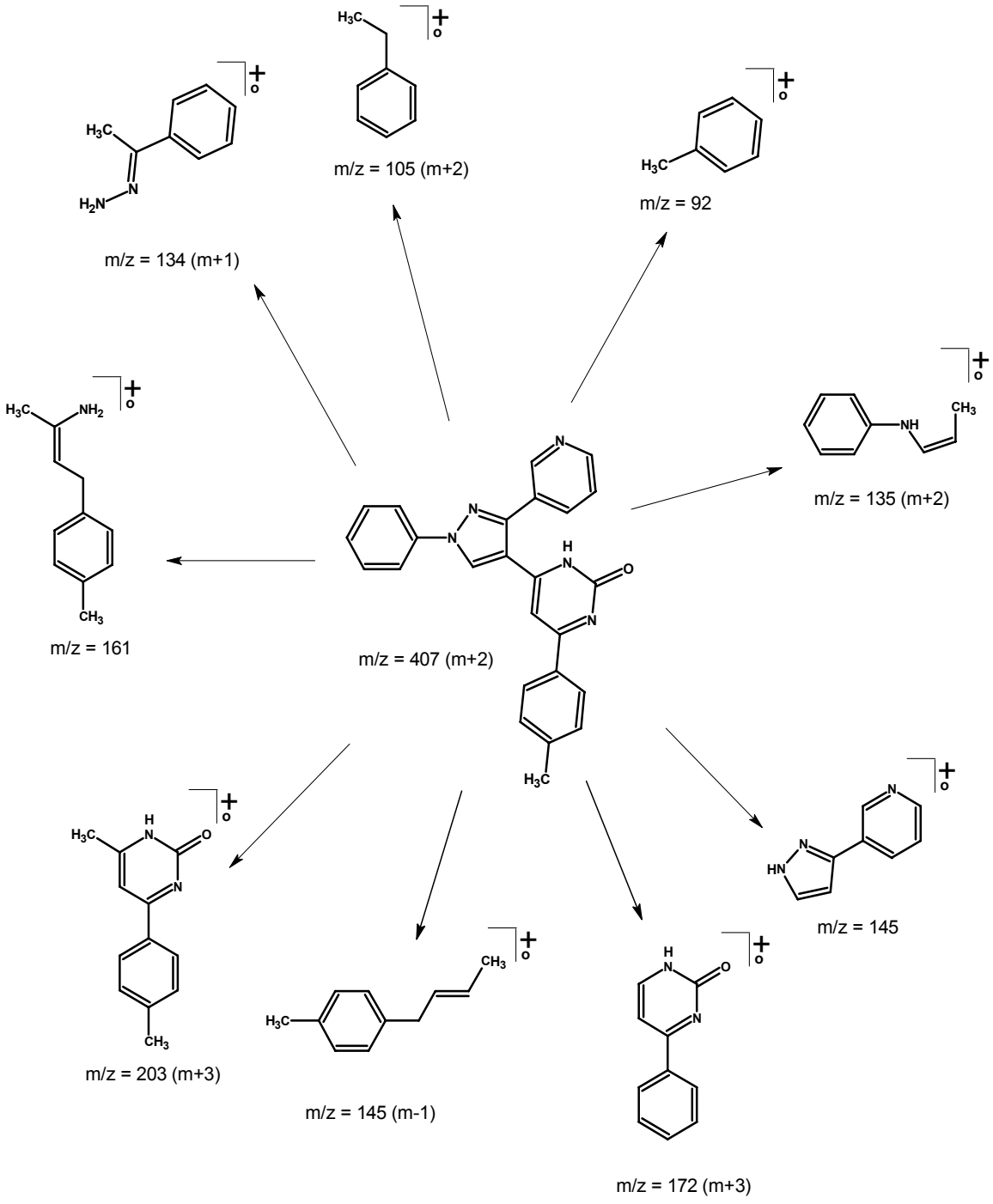
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.85	3H	singlet	Ar-OCH_3	-
2	7.42-7.45	2H	doublet	Ar-Ha,a'	Jaa'=7.8
3	7.45-7.48	2H	doublet	Ar-Hb,b'	Jbb'=6.9
4	7.51-7.56	3H	multiplet	Ar-Hc,dd'	-
5	7.79-7.82	2H	doublet	Ar-He,e'	Jee'=8.01
		1H	singlet	Ar-Hl	-
6	7.99-8.09	1H	multiplet	Ar-Hh	-
7	8.25-8.27	1H	multiplet	Ar-Hj	-
8	8.57	1H	singlet	Ar-Hf	-
9	8.70-8.71	1H	doublet	Ar-Hk	-
10	9.13	1H	singlet	Ar-Hg	-
11	10.06	1H	singlet	-NH	-

EXPANDED AROMATIC REGION






m/z = 105 (m+2)
m/z = 92
m/z = 134 (m+1)
m/z = 135 (m+2)
m/z = 161
m/z = 407 (m+2)
m/z = 145
m/z = 203 (m+3)
m/z = 145 (m-1)
m/z = 172 (m+3)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-(p-TOLYL)-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONE

[A] Synthesis of 1-Phenyl-3-â-pyridyl-4-formyl pyrazole

See part-I, Section -I(B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one

See Part-I, Section-II (B).

[C] Synthesis of 6-(p-Tolyl)-4-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-one

To a mixture of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one (3.65 g, 0.01M) in 25 ml of absolute alcohol add al. KOH and refluxed for 12 hrs. at temp 70^{o}C The reaction product was poured into ice. The product was isolated and crystallised from ethanol Yield 54%, m.p. 232^{o}C ($C_{25}H_{21}N_5O$; Found : C, 74.01%; H, 4.69%; N, 17.24%; Requires :C, 74.06%; H, 4.72%; N, 17.27%;).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 4.

[D] Antimicrobial activity of 6-Aryl-4-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2,3-dihydropyrimidine-2-ones

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solutions are recorded in Graphical Chart No.4.

Antitubercular screening of the compounds of type(V) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-II (C) and the percentage of inhibition data of the compounds are recorded in Table No. 4a.

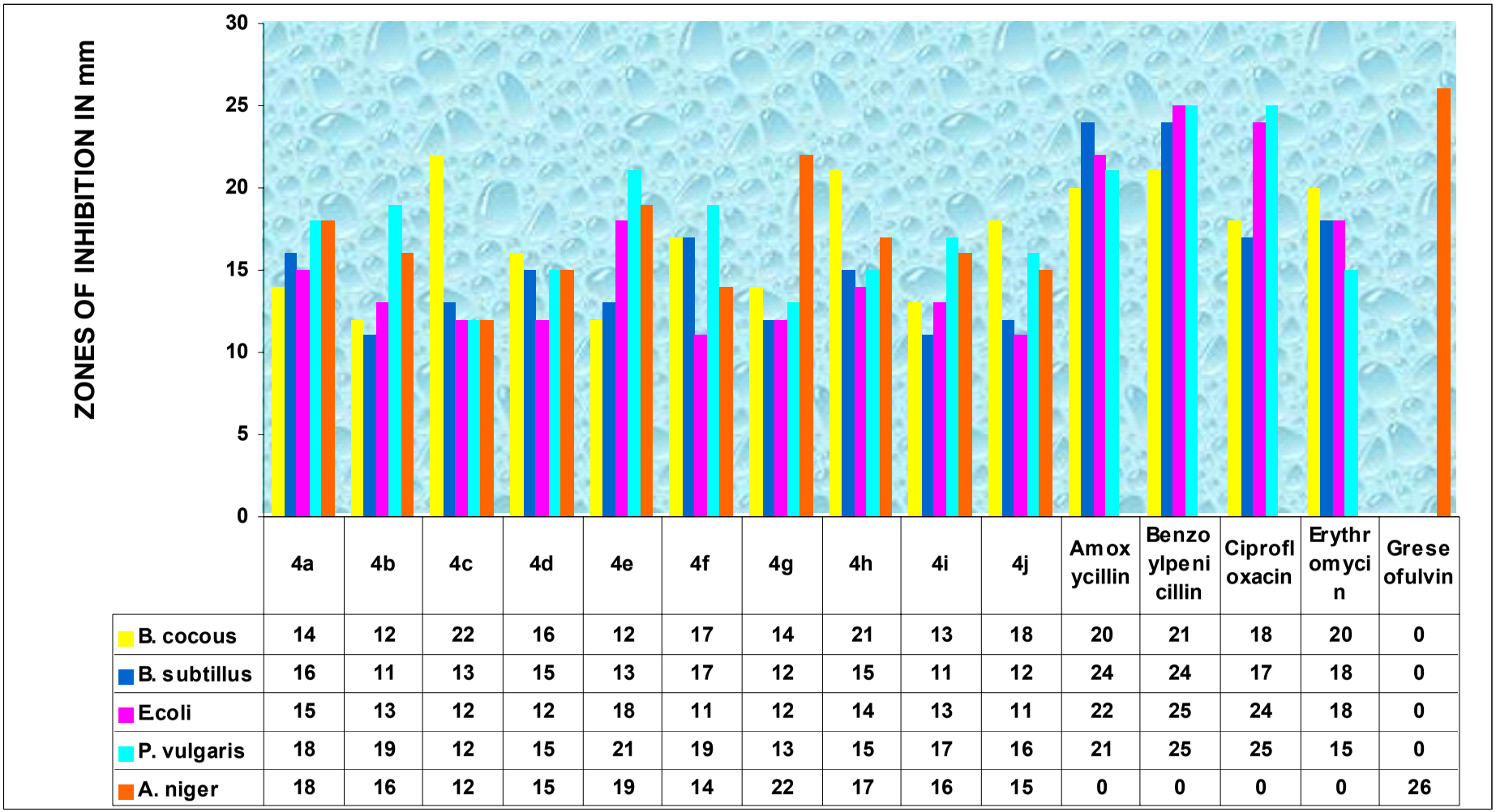
TABLE NO. 4 : PHYSICAL CONSTANTS OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONES

	R	Molecular Formula	Molecular Weight	M.P. °C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
	2	3	4	5	6	7	8	9
4a	4-CH_3-C_6H_4-	$C_{25}H_{19}N_5O$	405	256	0.59	49	17.27	17.24
4b	4-OCH_3-C_6H_4-	$C_{25}H_{19}N_5O_2$	421	243	0.53	52	16.62	16.59
4c	2-OH-C_6H_4-	$C_{24}H_{17}N_5O_2$	407	210	0.45	47	17.19	17.17
4d	4-OH-C_6H_4-	$C_{24}H_{17}N_5O_2$	407	223	0.49	54	17.19	17.15
4e	4-Cl-C_6H_4-	$C_{24}H_{16}ClN_5O$	425.5	269	0.51	59	16.44	16.42
4f	4-F-C_6H_4-	$C_{24}H_{16}FN_5O$	409	237	0.37	49	17.11	17.09
4g	4-Br-C_6H_4-	$C_{24}H_{16}BrN_5O$	470	226	0.39	44	14.89	14.88
4h	3-NO_2-C_6H_4-	$C_{24}H_{16}N_6O_3$	436	250	0.42	40	19.26	19.24
4i	4-NO_2-C_6H_4-	$C_{24}H_{16}N_6O_3$	436	265	0.48	51	19.26	19.23
4j	4-NH_2-C_6H_4-	$C_{24}H_{18}N_6O$	406	192	0.60	55	20.68	20.66

*TLC Solvent System : Acetone : Benzene

3 : 7

GRAPHICAL CHART NO. 4 ; ANTIMICROBIAL ACTIVITY OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONES

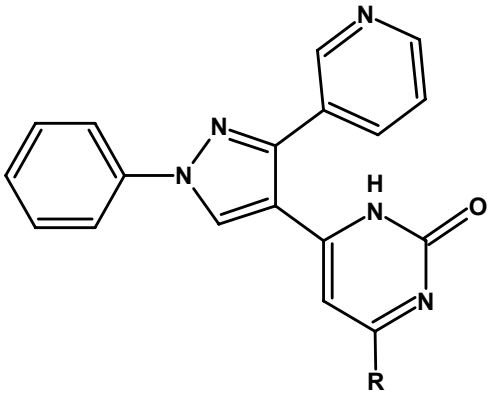


	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	14	12	22	16	12	17	14	21	13	18	20	21	18	20	0
B. subtillus	16	11	13	15	13	17	12	15	11	12	24	24	17	18	0
E.coli	15	13	12	12	18	11	12	14	13	11	22	25	24	18	0
P. vulgaris	18	19	12	15	21	19	13	15	17	16	21	25	25	15	0
A. niger	18	16	12	15	19	14	22	17	16	15	0	0	0	0	26

BIOLOGICAL EVALUATION OF 6-ARYL-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2,3-DIHYDROPYRIMIDINE-2-ONES

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
4c(22)	4f(17)	4e(18)	4e(21)	4g(22)
4h(21)	4g(16)	4b(19)	4e(19)	
4j(18)	4c(15)	4f(19)	4a(18)	
4f(17)	4h(16)	4a(18)	4h(17)	
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

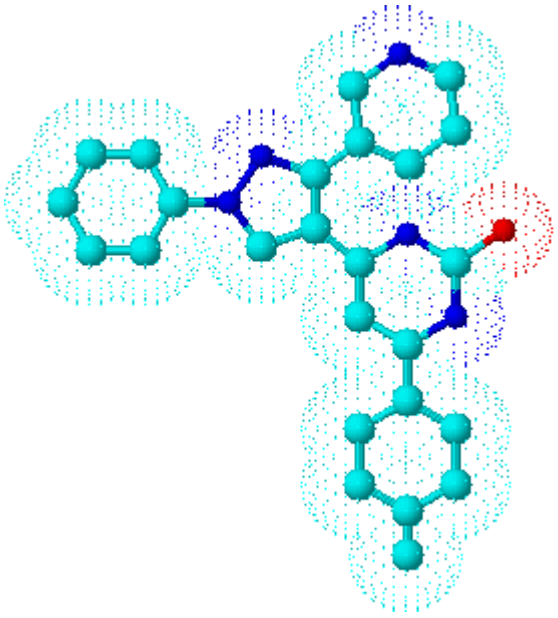
TABLE NO. 4a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

Sample ID	Corp ID	Where, R =	Assay	MTb Strain	MIC mg/ml	% Inhib	Activity	Comment
RKP-75	295743	4-NH_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	22	-	MIC Rifampin =
RKP-76	295744	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	53	-	0.25 mg/ml
RKP-77	295745	4-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	@ 98% Inhibition
RKP-78	295746	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	11	-	"
RKP-79	295747	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-80	295748	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	54	-	"
RKP-81	295749	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	50	-	"
RKP-82	295750	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
RKP-83	295751	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	16	-	"
RKP-84	295752	4-CH_3-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	13	-	"

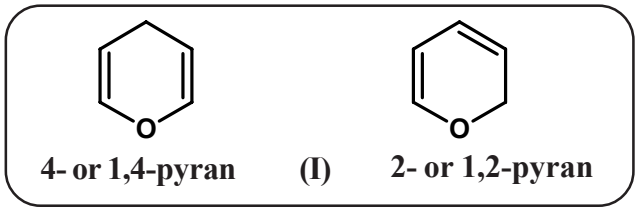


PART - III

STUDIES ON CYANOPYRANS

INTRODUCTION

The chemistry of pyran with different functional groups exhibit wide range of applications in the field of pharmaceuticals, dyes, insecticides and sweet smelling substances. Pyran ring system is also present in large number of natural coloured compounds in Vitamin E, hemorrhagic compound in cloves, in fish poisions, in certain alkaloids and other substances. Pyran is a doubly unsaturated six membered ring system with a single oxygen as hetero atom. The two double bonds may be conjugated as α or 1,2-pyran or isolated as in γ or 1,4-pyran.

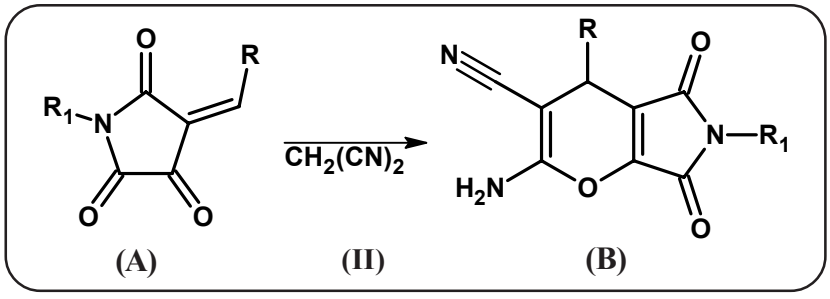


A degree of stabilisation of the pyran nucleus is achieved by substituting phenyl group in the 2 or 4 and preferably also in the 6 position.

SYNTHETIC ASPECT

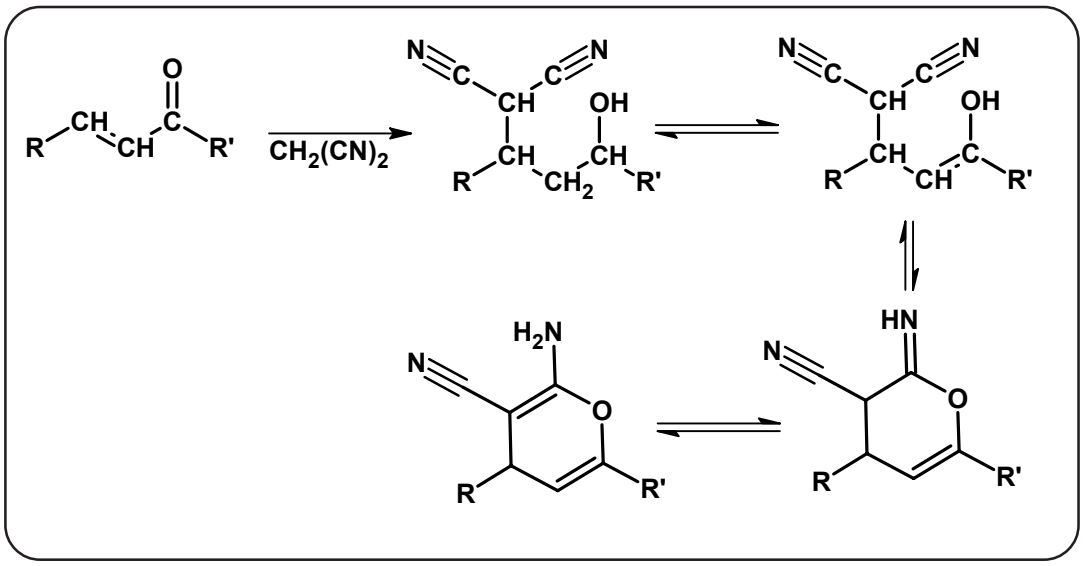
Various methods for the preparation of pyran derivatives have been cited in the literature[195-204].

1. Reaction between (A) with $CH_2(CN)_2$ led to the corresponding 2-amino-3-cyano-4H-pyrans (B)[205].



MECHANISM :

The reaction of malononitrile with α, β-unsaturated system leads to the formation of cyano 4H-pyran via Michael addition.

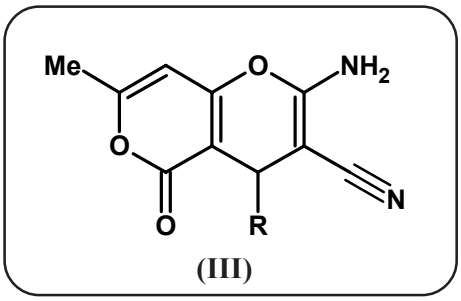


THERAPEUTIC IMPORTANCE

Literature survey revealed that various pyrans have resulted in many potential drugs and are known to possess a broad biological spectrum such as,

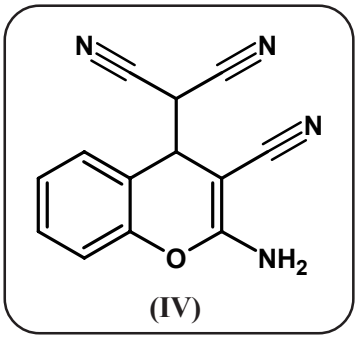
1. Anti HIV[206,207]
2. Antifungal[208-210]
3. Antiallergic[211]
4. Analgesic[212]
5. Antagonist[213,214]
6. Antitumor[215]
7. CNS active agent[216]
8. Cytotoxic[217]
9. Inhibitors of cell proliferation[218]
10. Gastric acid secretion inhibitor[219]
11. Antimicrobial[220]
12. Hypolipidemic[221]
13. Antipyretic[222]
14. Antiinvasive[223]

Moreover, Fathy F. Abdel-Latif et. al.[224] have reported the synthesis of 2-amino-3-cyanopyran derivatives and studied their biological activity. Piao Minz, Zhu et. al.[225] have prepared biologically active 2-amino pyran derivatives. Sharanin Y. U. A. et. al.[226] have suggested new 2-amino-3-cyano-4Hpyran derivatives (III).



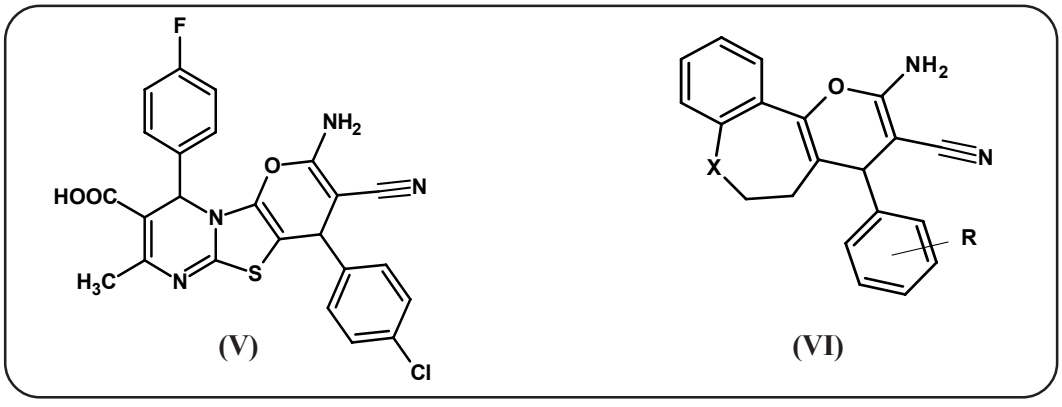
(III)

Zwaagstra Mariel et. al.[227] have newly synthesised pyran derivatives and tested for antiashamatic activity. Boyer Frederick et. al.[228] have prepared some new-2-amino-3-cyano-4H-pyran and reported anti HIV agent and antiviral activity. Some of the pyran derivatives have been patented for their use as antihypertensive[229], antiestogens[230], antagonist[231,232], antitumor[233] and antiviral[234] activities. Synthesis and biological activity of pyran ring system have been reported by O'Brien et. al.[235].



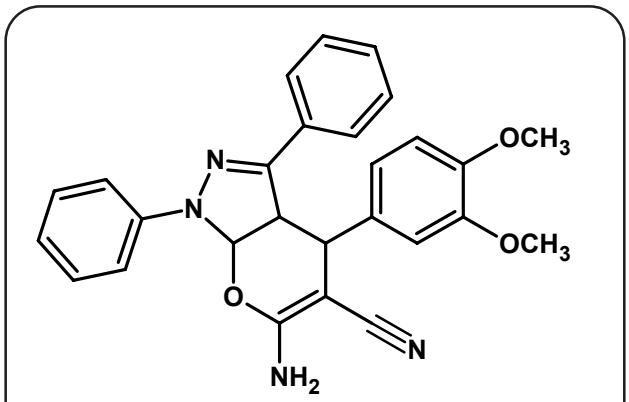
(IV)

Synthesis and anticancer activity of pyran (V) containing flourine have been reported by Mohamed S. Abd et. al.[236] 4H-pyran of type (VI) were prepared to enhance the anticancer and anti HIV activity.



(V) (VI)

El-Subbagh and co-worker[237] have synthesised cyanopyran derivatives and showed their antiviral activity. Corbou Romuld et. al.[238] have synthesised cyanopyran derivatives (VII) which have significant pharmacological activity.



(VII)

CONTRIBUTION FROM OUR LABORATORY

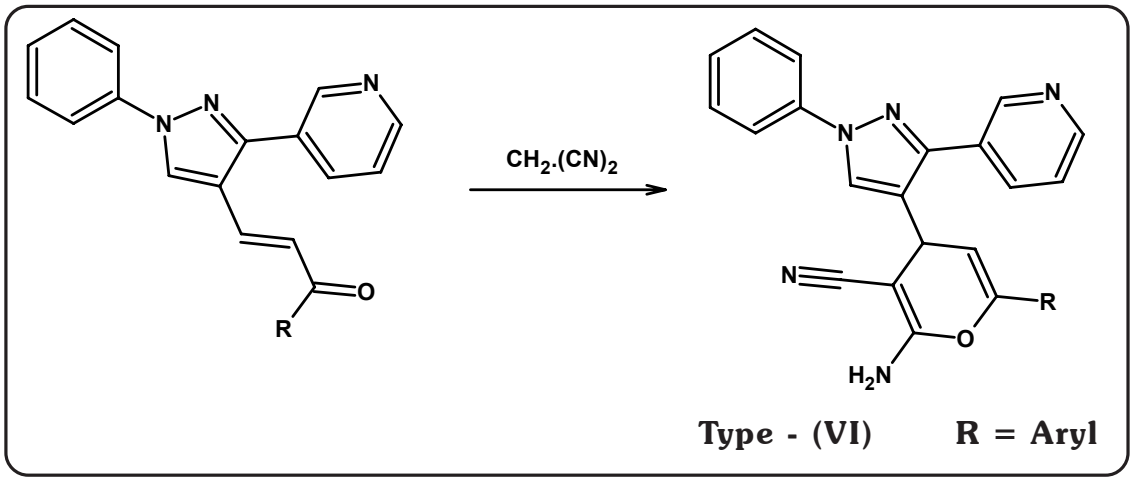
Parikh A. R. et. al.[239] have synthesised cyanopyrans bearing 2-chloro-6-bromoquinoline nucleus as a potential antimicrobial and anticancer agents. With a view to get better therapeutic agent, it was contemplated to synthesise pyran derivatives to enhance the overall activity of resulting compounds which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-6-ARYL-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-4H-PYRANS

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-6-ARYL-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-4H-PYRANS

In the past years, considerable evidence has been accumulated to demonstrate the efficiency of cyanopyrans. To further assess the potential of such a class of compounds cyanopyran derivatives of type (VI) have been synthesised by condensation of malononitrile with 1-Aryl-3-(1',N-phenyl-3'-β-pyridyl- pyrazol-4'-yl)-2-propen-1-ones.

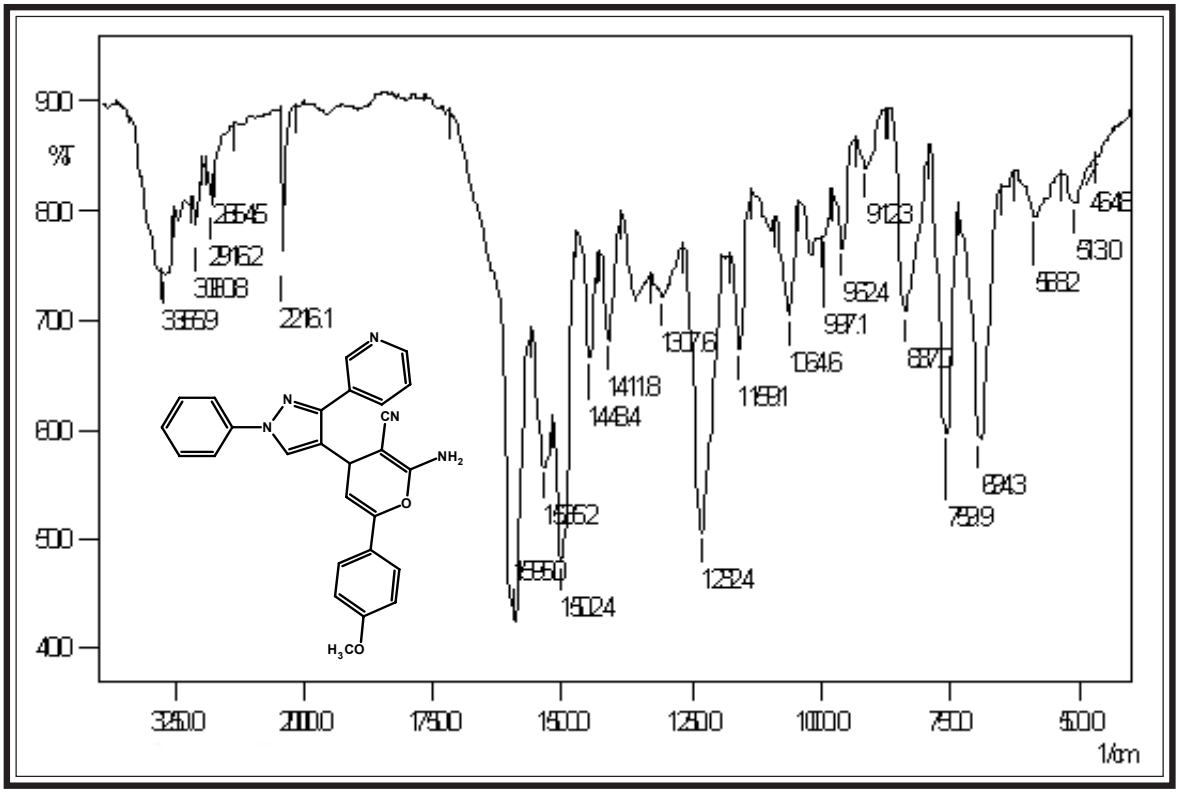


Type - (VI) **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.The mass spectra of 2-Amino-6-(p-anisyl)-3-cyano-4-[1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl]-4H-pyran give m/z = 447 (recorded on Page No. 88). The fragmentation is also explained (Page No. 89).

The products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activity of synthesised compounds were compared with standard drugs.

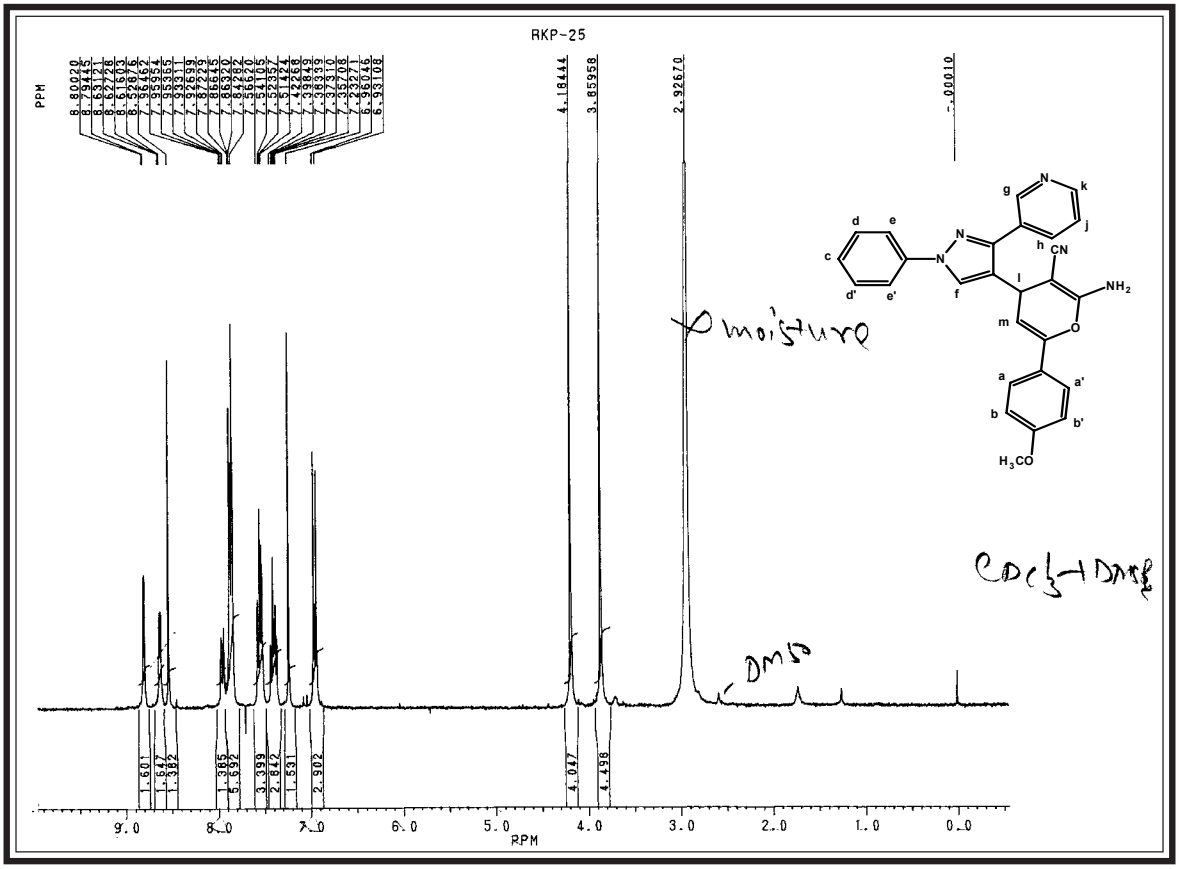
IR SPECTRAL STUDY OF 2-AMINO-6-(p-ANISYL)-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-4H-PYRAN



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2916	2995–2920	95
$-CH_3$	C – H str. (sym.)	2854	2880–2850	"
	C – H i.p. (def.)	1448	1470–1435	"
	C – H o.o.p. (def.)	1380	1385–1330	"
Aromatic	C – H str.	3060	3080–3010	96
	C – H i.p. (def.)	1064	1110–1000	"
	C – H o.o.p (def.)	837	835–810	"
Pyrazole	C = N str.	1595	1650–1600	96
moiety	C – N str.	1232	1350–1200	"
Ether	C- O-C str. (sym.)	1232	1275-1200	"
Ar-O-CH_3	C- O-C str. (sym.)	1064	1075-1020	"
		Overlapped		
Pyran	C = C str.	1595	1650-1520	95
		Overlapped		
	N- H str.	3355	1075–1020	"
	N- H def.	1595	1075–1020	"
	C≡N str.	2216	2240-2210	"

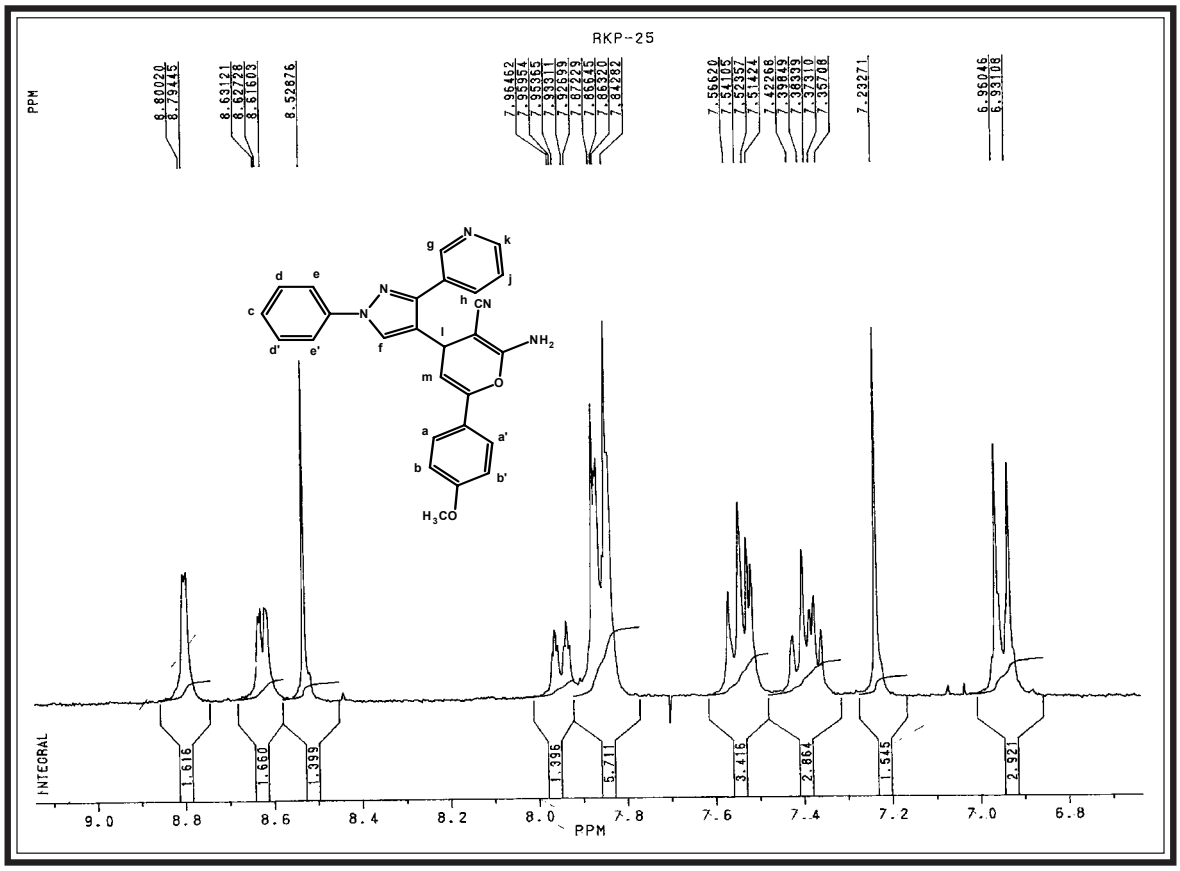
PMR SPECTRAL STUDY OF 2-AMINO-6-(p-ANISYL)-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-4H-PYRAN

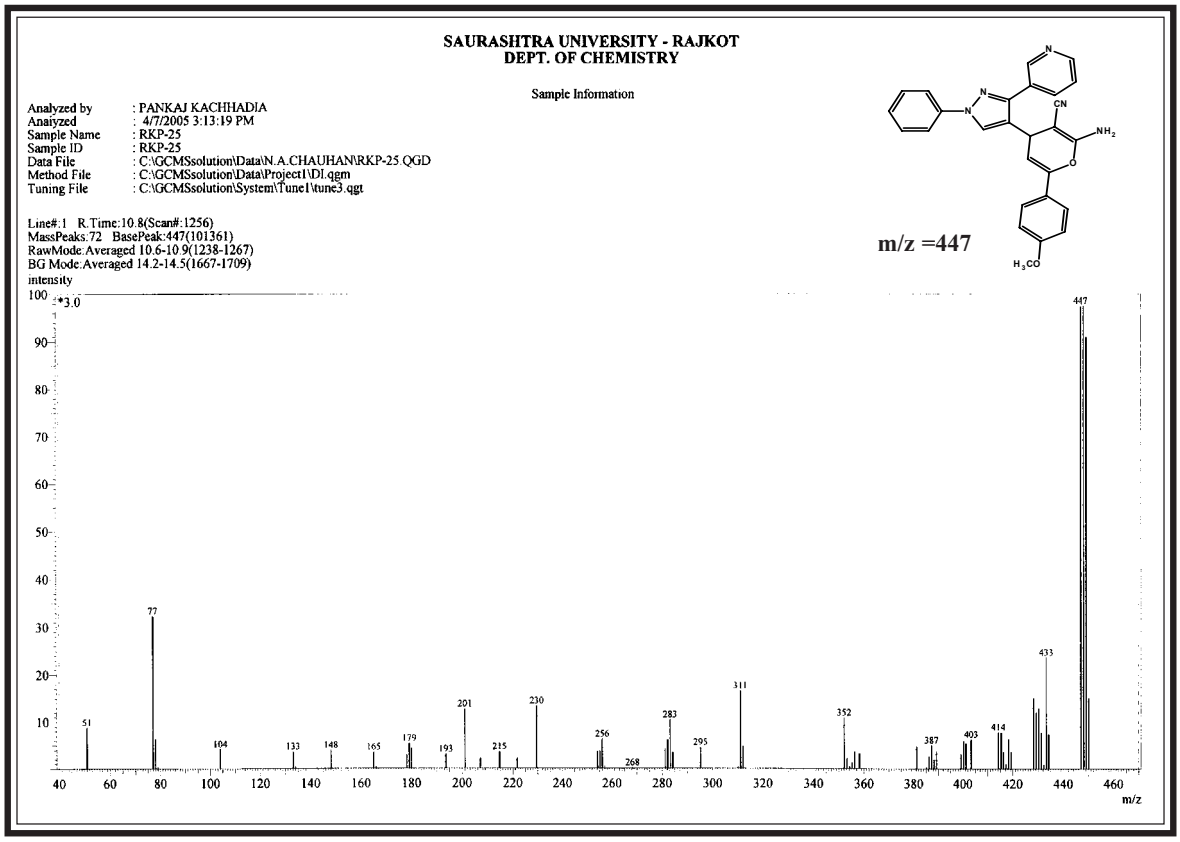


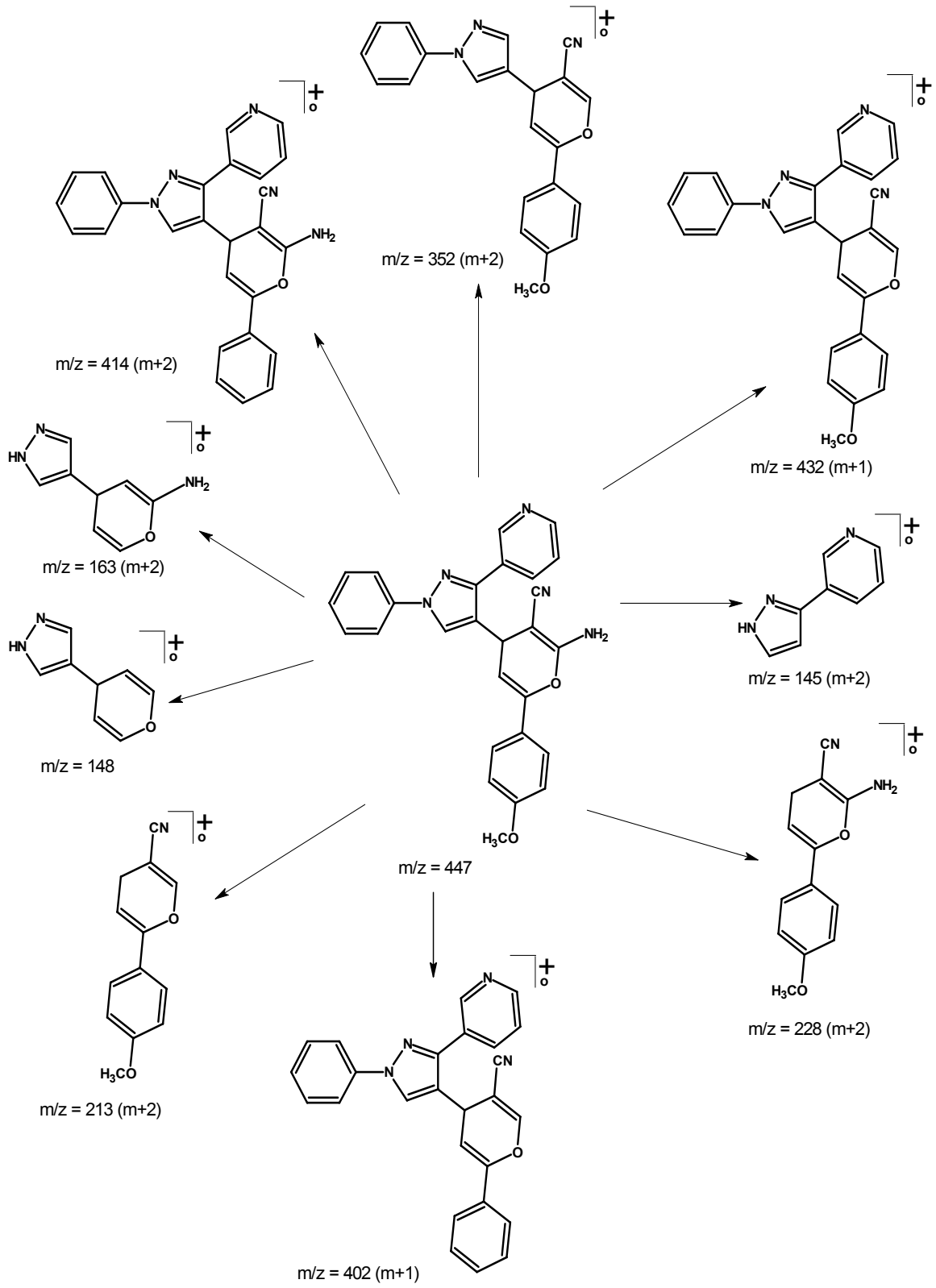
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.85	3H	singlet	Ar-OCH_3	-
2	4.18	1H	singlet	Ar-Hl	-
3	6.93-6.96	2H	doublet	Ar-Hbb'	Jbb'=8.8
4	7.35-7.42	2H	multiplet	Ar-Hh,m	-
5	7.51-7.56	3H	multiplet	Ar-Hc,d,d'	-
6	7.84-7.87	4H	doublet	Ar-Haa'	Jaa'=7.9
			doublet	Ar-Hee'	Jee'=8.0
7	7.92-7.97	1H	d,d	Ar-Hj	Jjh=9.4
					Jjk'=9.7
8	8.52	1H	singlet	Ar-Hf	-
9	8.61-8.63	1H	doublet	Ar-Hk	Jij=5.6
10	8.8	1H	singlet	Ar-Hg	-

EXPANDED AROMATIC REGION






m/z = 352 (m+2)
m/z = 414 (m+2)
m/z = 432 (m+1)
m/z = 163 (m+2)
m/z = 145 (m+2)
m/z = 148
m/z = 447
m/z = 213 (m+2)
m/z = 228 (m+2)
m/z = 402 (m+1)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-6-ARYL-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-4H-PYRANS

[A] Synthesis of 1,N-Phenyl-3-â-pyridyl-4-formyl pyrazole

See Part-I, Section-I (B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one

See Part-I, Section-II (B).

[C] Synthesis of 2-Amino-6-(p-tolyl)-3-cyano-4-[1',N-phenyl-3'-â-pyridyl-1H-pyrazol-4'-yl]-4H-pyran

A mixture of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one (3.65 g, 0.01 M), malononitrile (0.66 g, 0.01 M) and 2 ml pyridine dissolved in absoulte alcohol was refluxed for 8 hrs. in water bath at 70^{o}C. The reaction product was poured into ice, crude product was isolated, crystallised from ethanol. Yield 47%, m.p. 196^{o}C ($C_{27}H_{21}N_5O$; Found : C, 75.10%; H, 4.86%; N, 16.20%; Requires : C, 75.16%; H, 4.91%; N, 16.23%).

Similarly other cyanopyrans have been obtained. The physical data are recorded in Table No. 5.

[D] Antimicrobial activity of 2-Amino-6-aryl-3-cyano-4-[1',N-phenyl-3'-â-pyridyl-1H-pyrazol-4'-yl]-4H-pyrans

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solutions are recorded in Graphical Chart No.5.

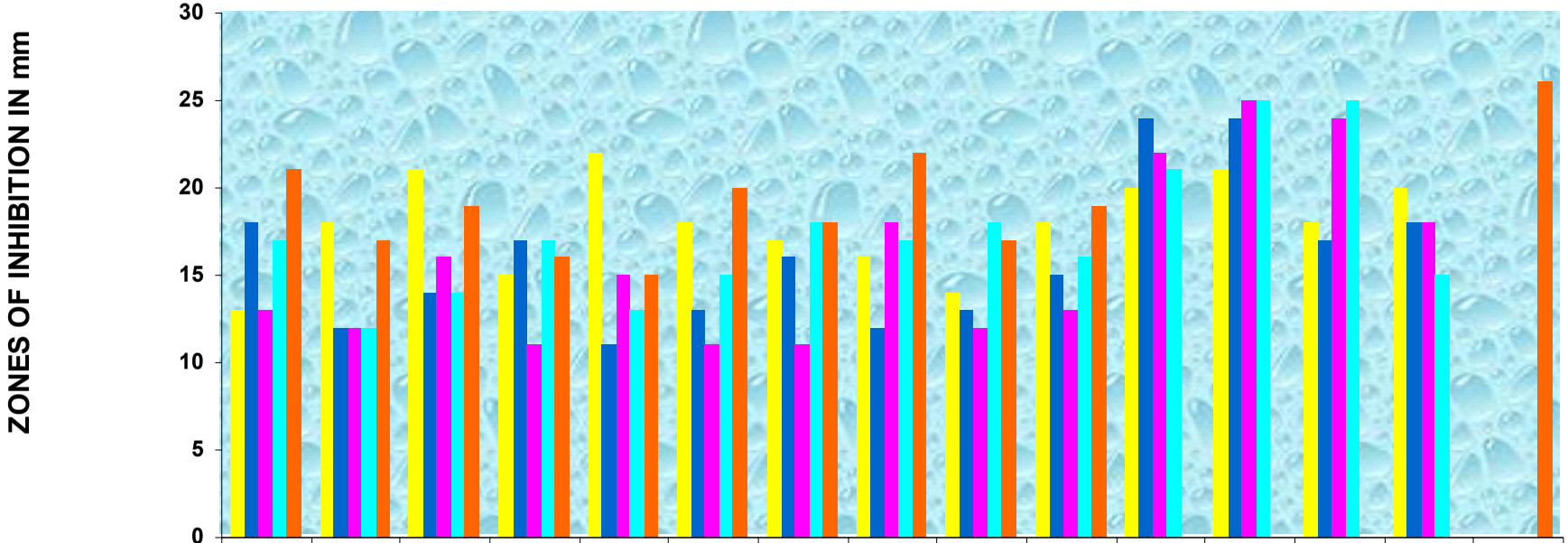
TABLE NO. 5 : PHYSICAL CONSTANTS OF 2-AMINO-6-ARYL-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-4H-PYRANS

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
5a	4-CH_3-C_6H_4-	$C_{27}H_{21}N_5O$	431	196	0.63	47	16.23	16.20
5b	4-OCH_3-C_6H_4-	$C_{27}H_{21}N_5O_2$	447	210	0.55	55	15.65	15.62
5c	2-OH-C_6H_4-	$C_{26}H_{19}N_5O_2$	433	240	0.57	43	16.16	16.14
5d	4-OH-C_6H_4-	$C_{26}H_{19}N_5O_2$	433	225	0.60	57	16.16	16.13
5e	4-Cl-C_6H_4-	$C_{26}H_{18}ClN_5O$	451.5	252	0.47	69	15.50	15.47
5f	4-F-C_6H_4-	$C_{26}H_{18}FN_5O$	435	192	0.54	60	16.08	16.05
5g	4-Br-C_6H_4-	$C_{26}H_{18}BrN_5O$	496	213	0.43	59	14.11	14.08
5h	3-NO_2-C_6H_4-	$C_{26}H_{18}N_6O_3$	462	184	0.49	43	18.17	18.13
5i	4-NO_2-C_6H_4-	$C_{26}H_{18}N_6O_3$	462	203	0.53	45	18.17	18.15
5j	4-NH_2-C_6H_4-	$C_{26}H_{20}N_6O$	432	215	0.67	52	19.43	19.41

*TLC Solvent System : Acetone : Benzene

3 : 7

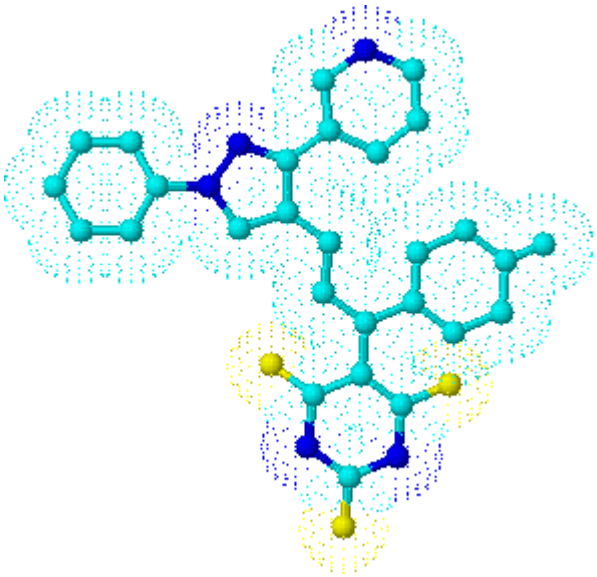
GRAPHICAL CHART NO. 5 : ANTIMICRONIAL ACTIVITY OF 2-AMINO-6-ARYL-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-1H-PYRAZOL-4'-YL]-4H-PYRANS



	5a	5b	5c	5d	5e	5f	5g	5h	5l	5j	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	13	18	21	15	22	18	17	16	14	18	20	21	18	20	0
B. subtillus	18	12	14	17	11	13	16	12	13	15	24	24	17	18	0
E.coli	13	12	16	11	15	11	11	18	12	13	22	25	24	18	0
P. vulgaris	17	12	14	17	13	15	18	17	18	16	21	25	25	15	0
A. niger	21	17	19	16	15	20	18	22	17	19	0	0	0	0	26

BIOLOGICAL EVALUATION OF 2-AMINO-6-ARYL-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-1H-PYRAZOL-4'-YL]-4H-PYRANS

	Antibacterial Activity zone of inhibition in mm			Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
5e(22)	5f(18)	5h(18)	5g(18)	5h(22)
5c(21)	5d(17)		5i(18)	5a(21)
5b(18)			5a(17)	5f(20)
5f(18)			5d(17)	5c(19)
5j(18)				5j(19)
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	



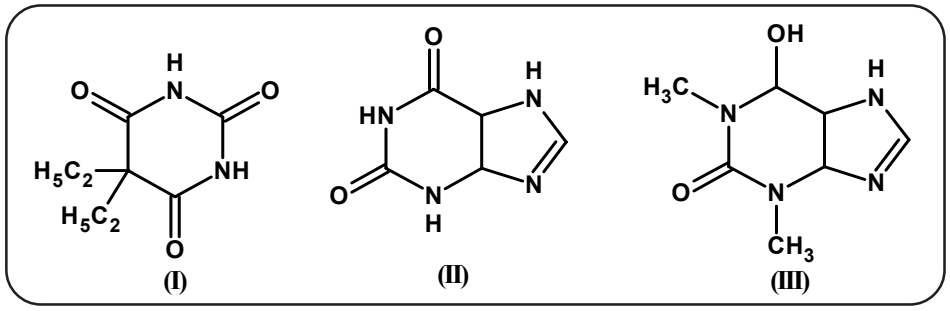
PART - IV

STUDIES ON BARBITONES

INTRODUCTION

Barbituric acid derivatives have gained prominance because of their potential pharmaceutical values. Many barbituric acid derivatives play vital role in many physiological action. Most important is the effect of barbiturates on the central nervous system. There are more than 40 synthetic drugs bearing barbituricacid, moiety in use recently. They possess diverse type of biological properties including hypnotic, sedatives, anticonvulsant, cardiovascular etc. The first member of hypnotic drugs series was barbital (I).

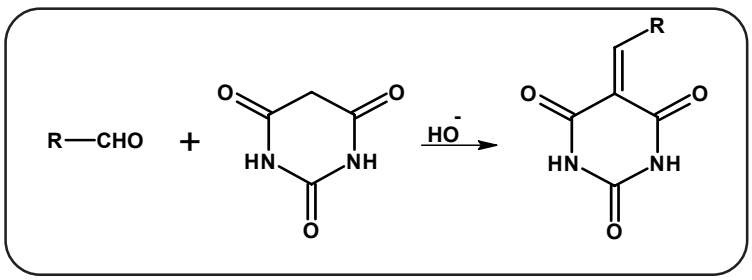
Barbituric acid ring system has been found in many natural products like alkaloids, which includes Xanthine (II) and Theophyline (III) are constituents of tea leaves. Theobromine is found in cocoa beans.



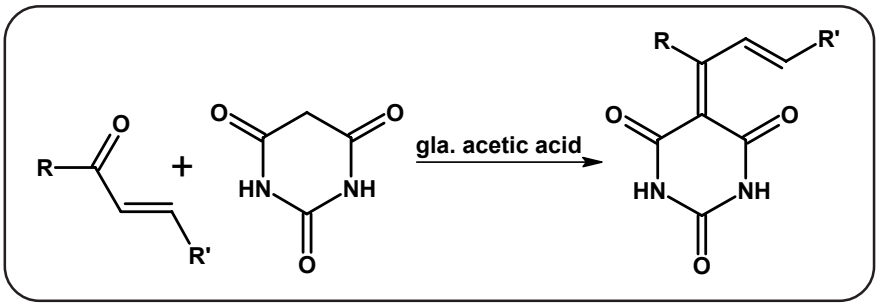
SYNTHETIC ASPECT

Different methods are used for the preparation of barbitones in literature[240,241].

1. Cao-Yun Weu et. al.[242] have prepared barbituric acid derivatives by the action of different aldehydes with barbituric acid in basic media.



2. M. R. Mahmoud et. al.[243] have synthesised barbituric acid derivatives from chalcone.

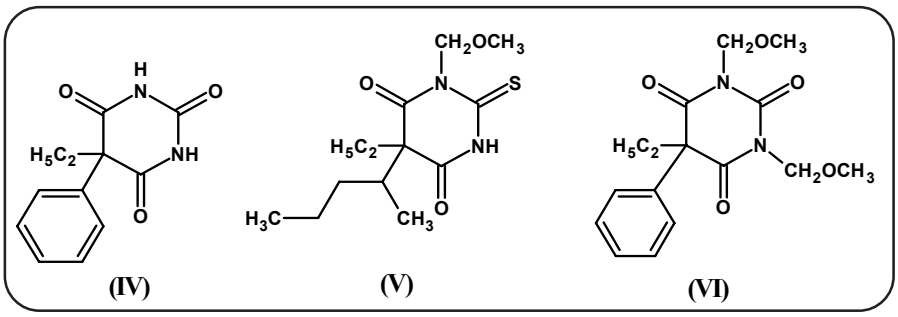


3. Ogus Funda et. al.[244] have synthesised barbiturates by the reaction between acetone and barbituric acid.

THERAPEUTIC IMPORTANCE

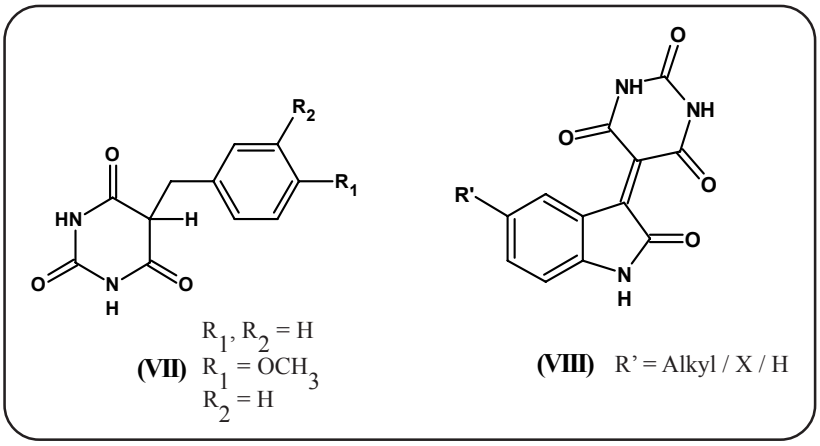
Barbituric acid derivatives demonstrate a very broad spectrum of biological activity, because of their structural relationship with nucleic acids, viz. uracil, thymine and cytosine. Perhaps barbituric acid derivatives are most widely used pyrimidines in medicinal chemistry.

Phenobarbitone (IV) possess sedative and hypnotic activities, thiopentone (V) is a useful local anaesthetic while Eterobarb (VI) is an anticonvulsant drug.



Carbubarb[245] is a barbituric acid derivative, which is used as a veternary anaesthetics. Some isoxazole pyrimidine derivatives have been studied because of their potential as as pesticidal[246,247] activity. Some barbiturates showing cardiovascular[248-250] and analgesic and antiinflammatory activities[251] have been reported.

Ulf Wellmar et. al.[252] have synthesised some uracil derivatives and screened for antiviral activity[253,254]. Raymond et. al.[255] investigated some barbiturates (VII), showing anticancer activity while Mahmoud et. al.[256] reported their antimicrobial activity.



(VII) R_1, R_2 = H, R_1 = OCH_3, R_2 = H

(VIII) R' = Alkyl / X / H

Some isoxazolo pyrimidine derivatives have been extensively studied and reported as antagonist[257] and antitumor[258] agents. Agricultural activity of 5-(3-benzylthiazolidin-2-ylidene)-1,3-dimethyl hexahydro pyrimidine-2,4,6-trione was reported by Wolf-Gang et. al.[259] Harbicidal and insecticidal activity of barbiturates was documented by Andre Roland and co-workers[260]. Omar M. T.[261] have showed barbitone derivatives demonstrating antimicrobial activity. Sakai and co-workers[262] has synthesised some new barbitones which are assessed for bone and cartilage diseases. R. T. Pardasani and co-workers[263] have described some new isatylidene barbitones (VIII) and tested their antibacterial activity.

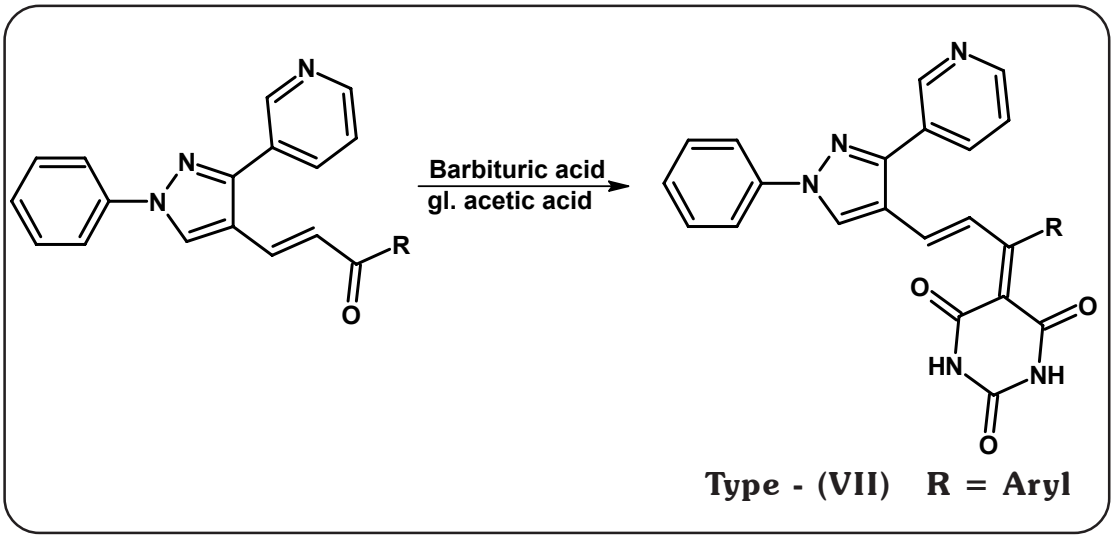
Vital contribution of barbituric acid ring system to the medicinal chemistry as an active constituent of hypnotics and sedatives made chemists to explore for its other derivatives as therapeutic agents. Accordingly several derivatives of barbituric acid have been designed as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 5-[1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6 (1H,3H,5H)-TRIONES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 5-[1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONES

Barbiturates are known to play an important role in medicinal chemistry because of their effect on central nervous system. The first member of hypnotic drugs series was barbital. Considering this background, some new barbituric acid derivatives of type (VII) were prepared by the condensation of compounds of type (II) with barbituric acid in glacial acetic acid.

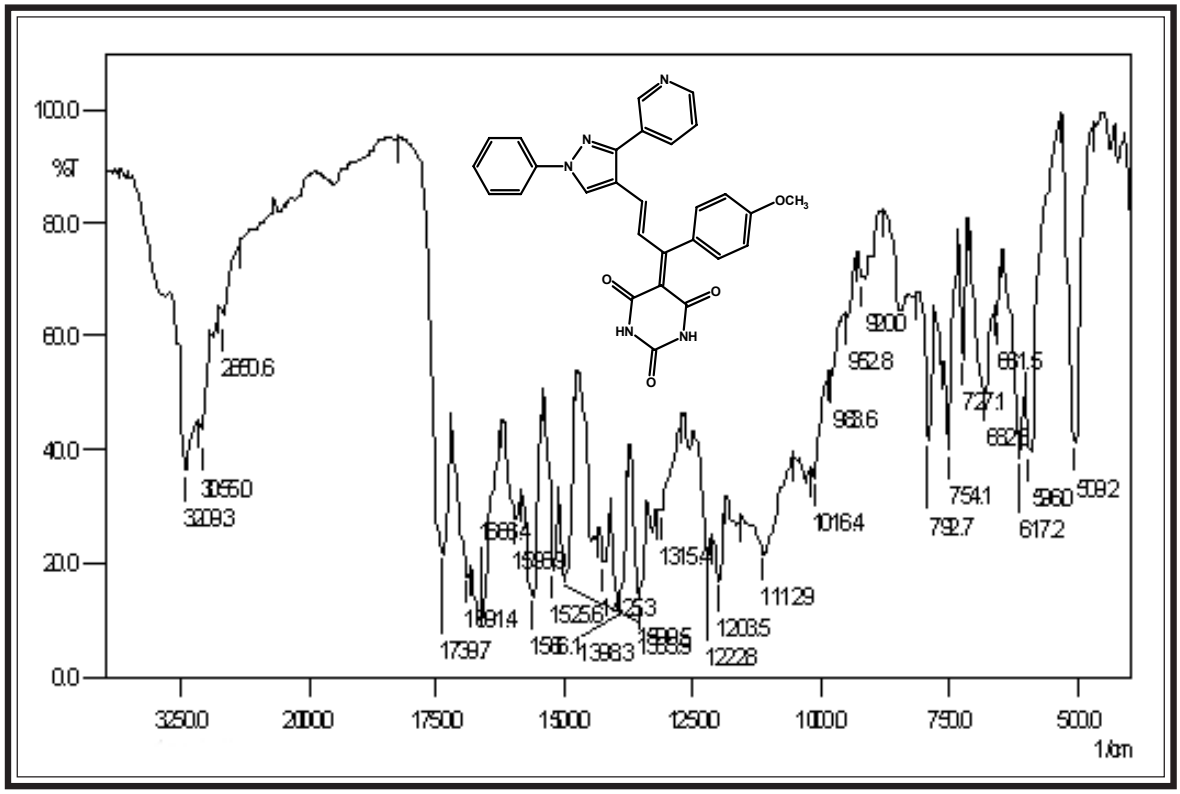


Type - (VII) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.The mass spectra of 5-[1-(p-Anisyl)-3-(1',N-phenyl-3'-â-pyridyl-1,H-pyrazol-4'-yl)-prop-2-enylidene]pyrimidine-2,4,6(1H,3H,5H)-trione give m/z = 491 (recorded on Page No. 100). The fragmentation is also explained (Page No.101).

The products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activities of synthesised compounds were compared with standard drugs.

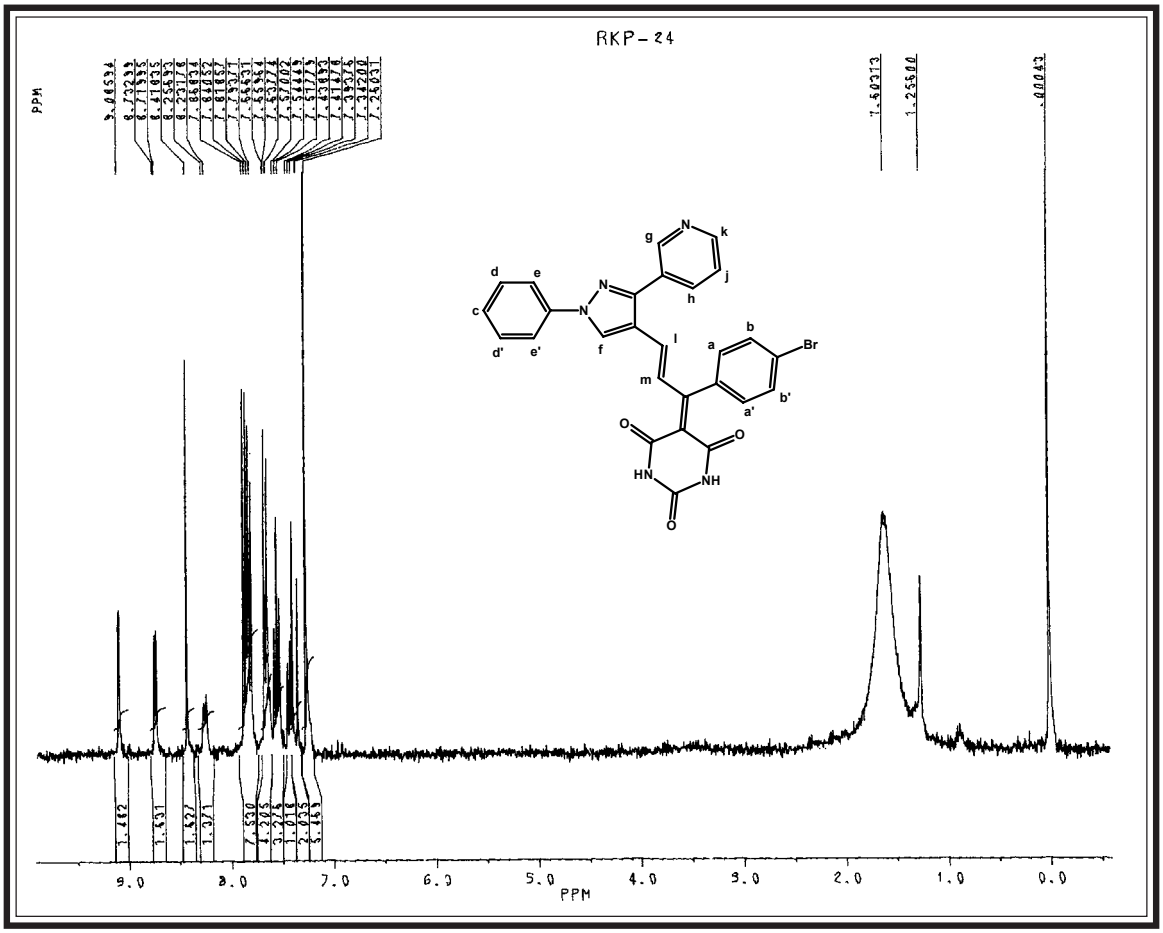
IR SPECTRAL STUDY OF 5-[1-(p-ANISYL)-3-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2953	2995–2920	95
$-CH_3$	C – H str. (sym.)	2850	2880–2850	"
	C – H i.p. (def.)	1425	1470–1435	"
	C – H o.o.p. (def.)	1355	1385–1330	"
Aromatic	C – H str.	3055	3080–3010	96
	C =C str.	1500	1540-1480	
	C – H i.p. (def.)	1016	1110–1000	"
	C – H o.o.p (def.)	829	835–810	"
Pyrazole	C = N str.	1598	1650–1600	96
moiety	C = C str.	1525	1585–1480	"
	C – N str.	1222	1350–1200	"
Barbitone	N- H str.	3209	3400-3200	
	C=O str.	1691	1700-1640	

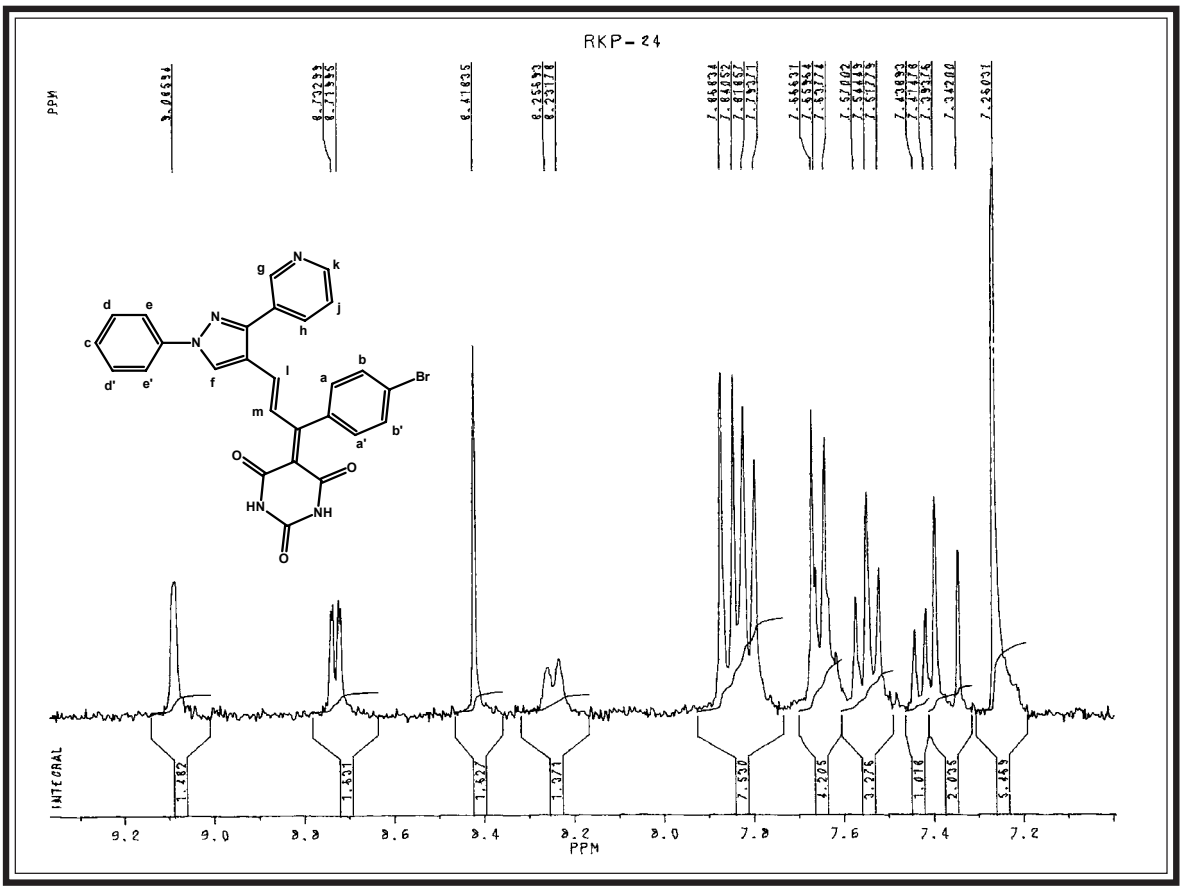
PMR SPECTRAL STUDY OF 5-[1-(p-BROMOPHENYL)-3-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONE

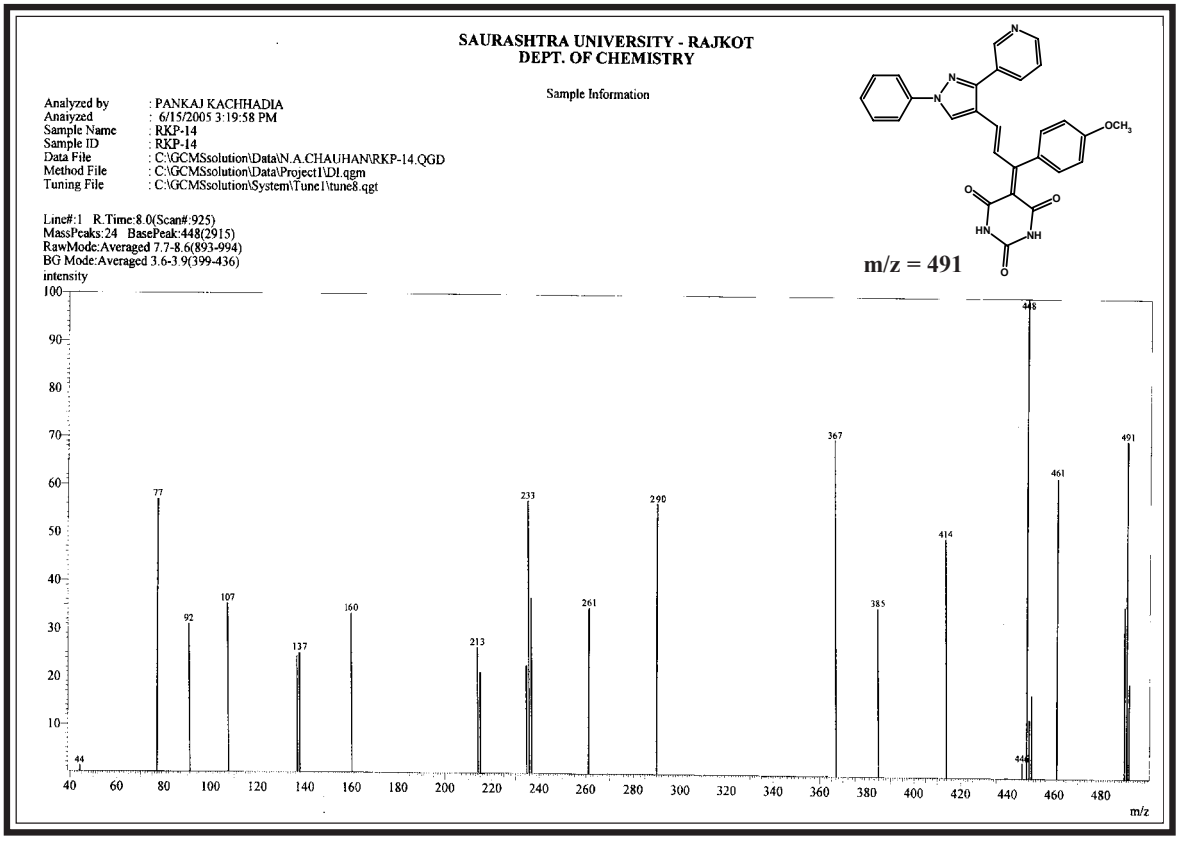


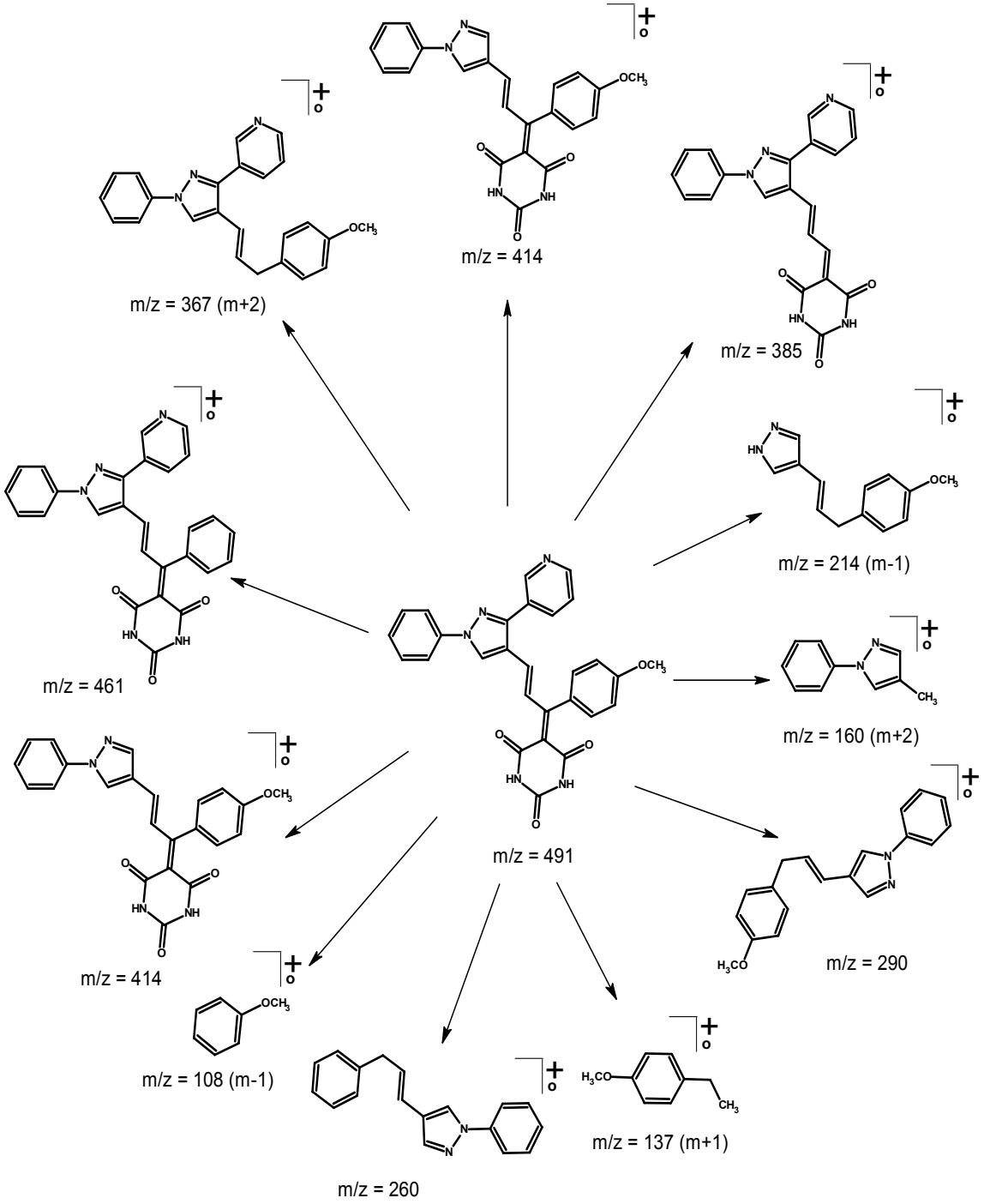
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	7.34-7.39	1H	doublet	Vin.Hm	Jml=15.5
2	7.51-7.57	3H	multiplet	Ar-Hh,aa'	-
3	7.63-7.67	3H	multiplet	Ar-Hc,dd'	-
4	7.79-7.81	2H	doublet	Ar-Hbb'	Jbb'=7.5
5	7.81-7.85	1H	doublet	Vin.Hl	Jlm=14.9
6	7.81-7.84	2H	doublet	Ar-Hee'	Jee'=8.3
7	8.23-8.25	1H	doublet	Ar-Hf	-
8	8.41	1H	singlet	Ar-Hk	-
9	8.71-8.73	1H	multiplet	Ar-Hg	-
10	9.08	1H	singlet	Ar-Hj	Jjk=7.60

EXPANDED AROMATIC REGION






m/z = 367 (m+2)
m/z = 414
m/z = 385
m/z = 461
m/z = 214 (m-1)
m/z = 160 (m+2)
m/z = 491
m/z = 414
m/z = 290
m/z = 108 (m-1)
m/z = 137 (m+1)
m/z = 260

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 5-[1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONES

[A] Synthesis of 1,N-Phenyl-3-â-pyridyl-4-formyl pyrazole

See Part-I, Section-I (B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-II (B).

[C] Synthesis of 5-[1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-1,H-pyrazol-4'-yl)-prop-2-enylidene]pyrimidine-2,4,6(1H,3H,5H)-trione

A mixture of 1-(p-Tolyl)-3-(1'-N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-one (3.65 g, 0.01 M) in ethanol & barbituric acid (1.28 g, 0.01 M)in glacial acetic acid was refluxed for 8 hrs. on oil bath. The reaction product was poured into ice, crude product was isolated, crystallised from ethanol. Yield 70%, m.p. 196^{o}C ($C_{28}H_{21}N_5O_3$; Found : C, 70.68%; H, 4.41%; N, 14.70%; Requires : C, 70.73%; H, 4.45%; N, 14.73%).

Similarly other cyanopyrans have been obtained. The physical data are recorded in Table No. 6.

[D] Antimicrobial activity of 5-[1-Aryl-3-(1',N-phenyl-3'-â-pyridyl-1,H-pyrazol-4'-yl)-prop-2-enylidene]pyrimidine-2,4,6(1H,3H,5H)-triones

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solutions are recorded in Graphical Chart No.6.

Antitubercular screening of the compounds of type(V) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-II (C) and the percentage of inhibition data of the compounds are recorded in Table No. 6a.

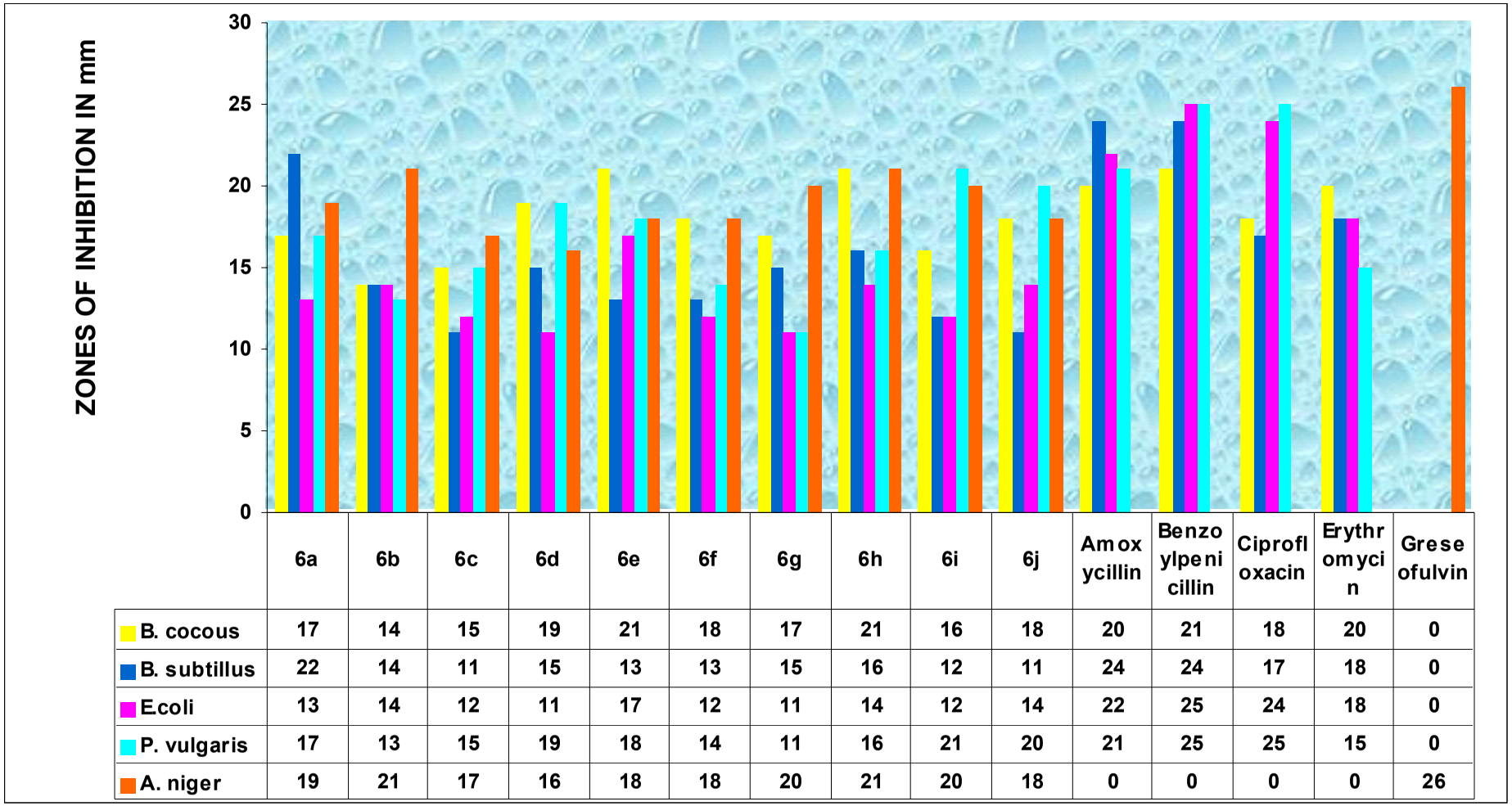
TABLE NO. 6 : PHYSICAL CONSTANTS OF 5-[1-ARYL-3- (1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. ^{o}C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
6a	4-CH_3-C_6H_4-	$C_{28}H_{21}N_5O_3$	475	272	0.48	70	14.73	14.70
6b	4-OCH_3-C_6H_4-	$C_{28}H_{21}N_5O_4$	491	228	0.52	65	14.25	14.24
6c	2-OH-C_6H_4-	$C_{27}H_{19}N_5O_4$	477	186	0.39	59	14.67	14.65
6d	4-OH-C_6H_4-	$C_{27}H_{19}N_5O_4$	477	210	0.47	71	14.67	14.64
6e	4-Cl-C_6H_4-	$C_{27}H_{18}ClN_5O_3$	495.5	224	0.58	67	14.12	14.09
6f	4-F-C_6H_4-	$C_{27}H_{18}FN_5O_3$	479	165	0.42	61	14.61	14.59
6g	4-Br-C_6H_4-	$C_{27}H_{18}BrN_5O_3$	540	226	0.53	57	12.96	12.95
6h	3-NO_2-C_6H_4-	$C_{27}H_{18}N_6O_5$	506	160	0.49	54	16.59	16.57
6i	4-NO_2-C_6H_4-	$C_{27}H_{18}N_6O_5$	506	239	0.62	58	16.59	16.56
6j	4-NH_2-C_6H_4-	$C_{27}H_{20}N_6O_3$	476	208	0.60	47	17.64	17.62

*TLC Solvent System : Acetone : Benzene

2 : 8

GRAPHICAL CHART NO. 6 : ANTIMICROBIAL ACTIVITY OF 5-[1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL -4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONES

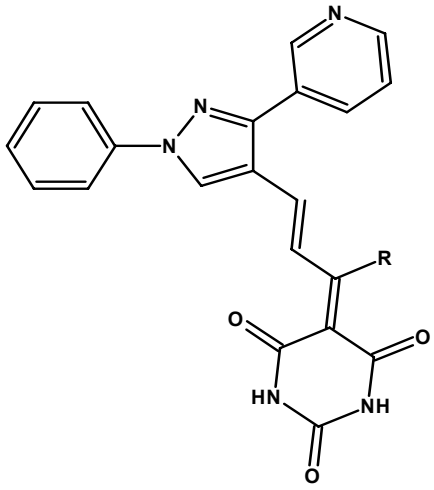


	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	17	14	15	19	21	18	17	21	16	18	20	21	18	20	0
B. subtillus	22	14	11	15	13	13	15	16	12	11	24	24	17	18	0
E.coli	13	14	12	11	17	12	11	14	12	14	22	25	24	18	0
P. vulgaris	17	13	15	19	18	14	11	16	21	20	21	25	25	15	0
A. niger	19	21	17	16	18	18	20	21	20	18	0	0	0	0	26

BIOLOGICAL EVALUATION OF 5-[1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)-PROP-2-ENYLIDENE]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONES

Antibacterial Activity zone of inhibition in mm			Antifungal Activity zone of inhibition in mm	
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
6e(21)	6a(22)	6e(17)	6i(21)	6b(21)
6h(21)	6h(16)		6j(20)	6h(21)
6d(19)			6d(19)	6i(20)
6f(18)			6e(18)	6i(20)
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

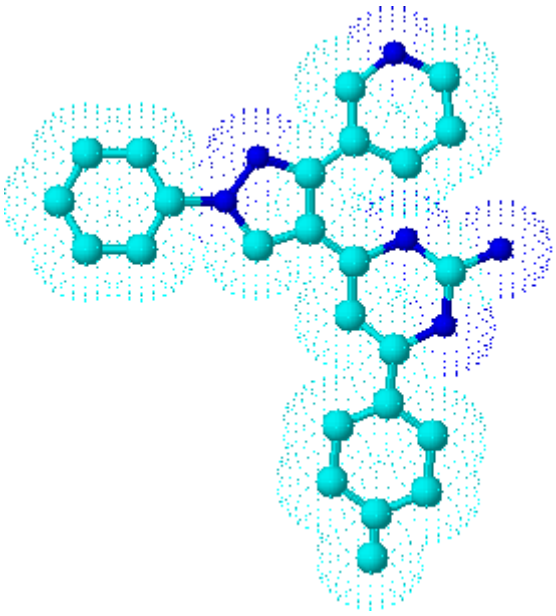
TABLE NO. 6a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC mg/ml*	*% Inhib*	*Activity*	*Comment*
RKP-33	295701	4-NH_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	1	-	MIC Rifampin =
RKP-34	295702	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	56	-	0.25 mg/ml
RKP-35	295703	4-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	@ 98% Inhibition
RKP-36	295704	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-37	295705	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	4	-	"
RKP-38	295706	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	41	-	"
RKP-39	295707	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-40	295708	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	6	-	"
RKP-41	295709	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	8	-	"
RKP-42	295710	4-CH_3-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"



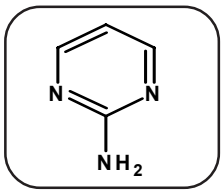
PART - V

STUDIES ON

AMINOPYRIMIDINES

INTRODUCTION

2-*A*minopyrimidine is the most important member of all the diazine as this ring system occurs widely in living organisms. Pyrimidine was first isolated by Gabriel and Colman in 1899. 2-Amino pyrimidine and its derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activities.

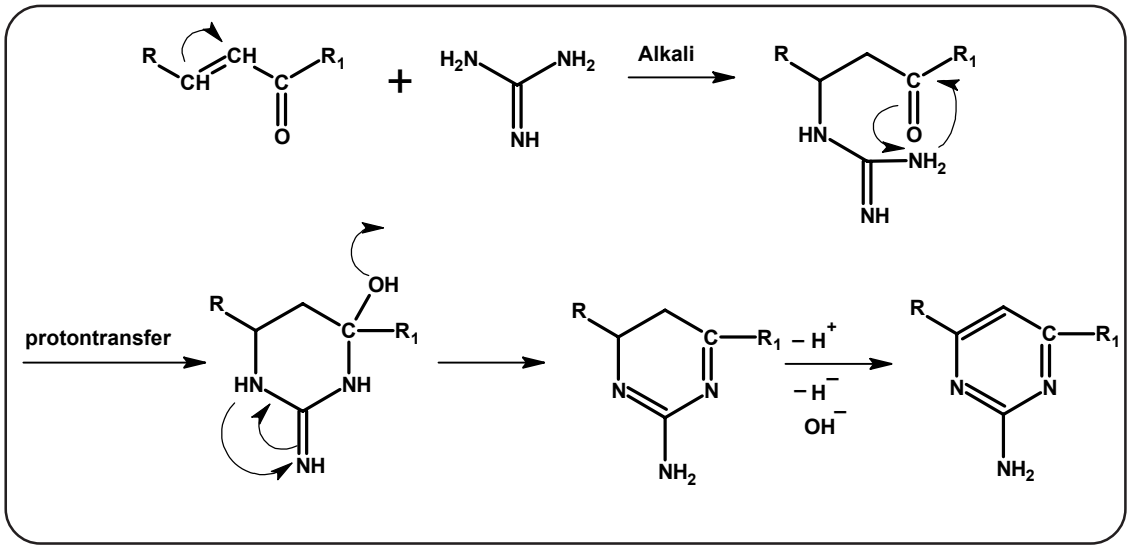


SYNTHETIC ASPECT :

1. The reaction of chalcone with guanidine hydrochloride in presence of potassium t-butoxide in t-butanol yielded corresponding 2-amino pyrimidine derivatives[264].
2. Abd-El-galil E. Amr[265] synthesised aminopyrimidines by the reaction of chalcones with guanidine hydrochloride in the presence of NaOH.
3. Rasaki[266] synthesised 2-amino-pyrimidine by the reaction of chalcone epoxides with guanidine carbonate in xylene.

REACTION MECHANISM :

The reaction proceeds through conjugated addition of guinidine hydrochloride to the α,β-unsaturated system. The bond formation take place between N-atom of guinidine hydrochloride and C-atom of chalcone.



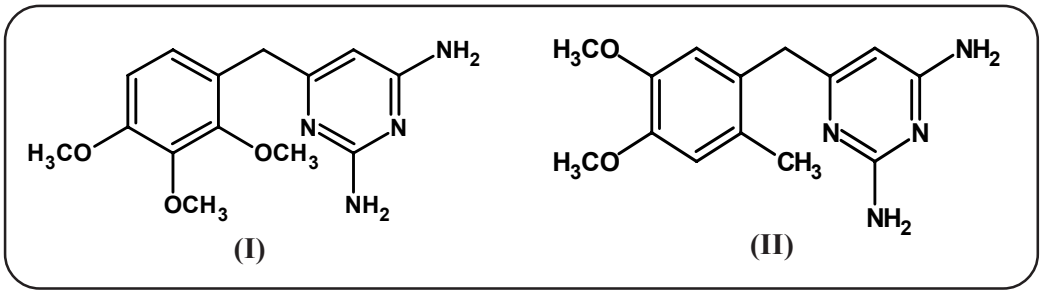
In the first step migration of electron takes place due to the more electronegativity of O-atom than C-atom. So carbon has positive charge while nitrogen atom looses proton so it aquires negative charge, with simultaneous removal of water.

THERAPEUTIC IMPORTANCE

2-Aminopyrimidines exhibit a wide spectrum of pharmacological activities like,

1. Antimicrobial[267,268]
2. Antitumor[269]
3. Inhibitor of celular proliferation[270]
4. Dopamine D4 antagonists[271]
5. Cardiovascular[272]
6. Inflammatory[273]
7. Antiviral[274]
8. Tyrosine kinase Inhibitor[275]
9. Adrenaline α-receptor bloker[276]

Large no of drugs possess aminopyrimidine ring system. Well-known antimalarial agents like trimethoprim (I) and pyrimethamine (II) possess pyrimidine ring system.



Hisaki Masakutsu[277] synthesised some aminopyrimidines which are useful in the treatment of rotaviral diseases. Robson C. et. al.[278] prepared aminopyrimidine derivatives as antifungal agents in P9P and MRP over expressive tumor cell lines. Leanne M. et. al.[279] have prepared aminopyrimidines and reported them as antiviral agent.

Yamada K [280]synthesised some aminopyrimidines and tested for endothelin antagonists. Suto, M. et. al.[281] prepared some amino pyrimidines which found to possess

antiinflammatory, anticancer, antirheumatoid activities. Gangjee A. et. al.[282] synthessied aminopyrimidines which possess antitumor activity. Ugarkar B. et. al.[283] found aminopyrimidines in the inhibition of cardiovascular and ceribrovascular disorders.

Hernandez et. al.[284] and Secrist J. et. al.[285] prepared aminopyrimidines showing antitumor activity. Glazier A. et. al.[286] and Singh J.[287] found aminopyrimidines as antiviral agents. Pan S.[288] prepared 2-methylthio-4-amino-6-(3,5-diacetylphenyl-amino)-pyrimidines. Which show anti HIV activity in H9 cell cultures. Aminopyrimidines derivatives also possess antimicrobial[289], antiHIV[290] and antitumor[291] activities.

Looking to the deversified activities exhibited and in continuation of our work on the synthesis of biologically active heterocycles, the synthesis and biological screening of aminopyrimidine derivatives have been described as under. Bargiotti, Alberto et. al.[292] prepared 1,7-disubstituted guanine derivatives for their therapeutic use as telomerase inhibitors & anticancer agent. Bargiatli, Alberto et. al.[293] prepared disubstitute 7,9-guaninium halides as telomerase inhibitors.

Peirre C. Wyss et. al.[294] prepared some novel aminopyrimidines as novel dihydrofolate reductase inhibitors. Aleem Gangjee et. al.[295] prepared some aminopyrimidines as potential dual inhibitors of thymidylate synthase & dihydrofalate reductase & as potential antitumor agents. Andre Rosowasky et. al.[296] prepared aminopyrimidines as potent & selective inhibitors of dihydrofalate reductase from three major opportunistic pathogens of AIDS. Tsutumi et. al.[297] prepared aminopyrimidines as addenosine receptor antagonists.

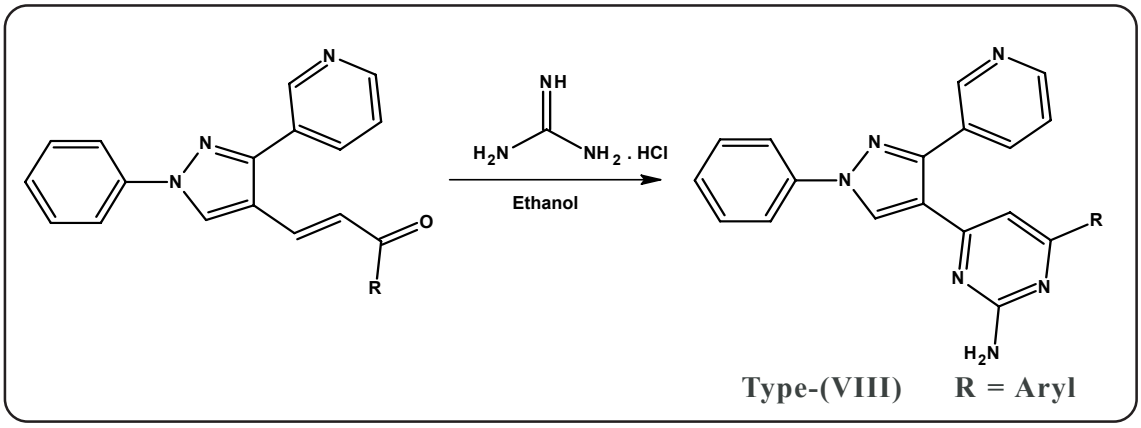
Looking to the interesting properties of Aminopyrimidines, we have synthesised some new aminopyrimidines, which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-4-ARYL-6-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOL-4'-YL)PYRIMIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-4-ARYL-6-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOLE-4'-YL)PYRIMIDINES

Looking to the interesting pharmacological and agriculture activity of pyrimidine ring system, it was considered worthwhile to synthesize some new 2-Amino-4-aryl-6-(1',N-phenyl-3'-â-pyridyl-1,H- pyrazole-4'-yl)pyrimidine of type (VIII) to study their biological activities. Amino pyrimidine derivatives have been prepared by the reaction of the chalcones of Type (II) with guanidine hydrochloride in presence of ethanol shown as under.

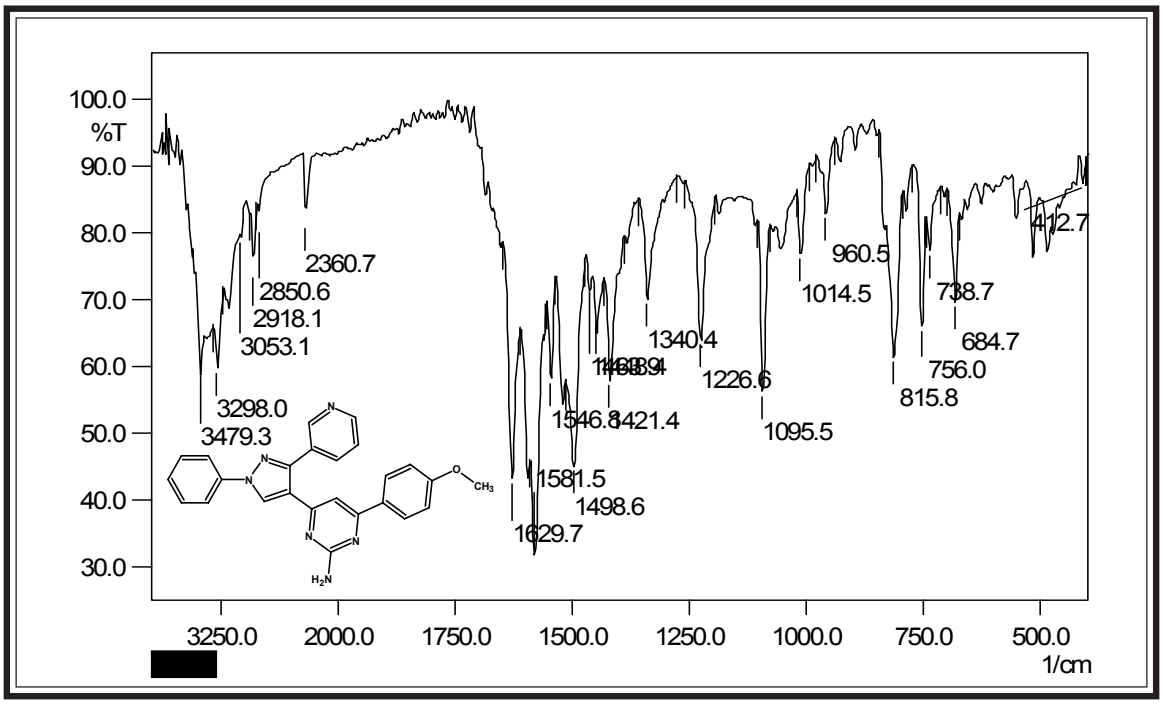


Type-(VIII) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H-nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy. The mass spectra of 2-Amino-4-(p-tolyl)-6-(1',N-phenyl-3'-â-pyridyl-1,H-pyrazole-4'-yl)pyrimidines give m/z = 404 (recorded on Page No. 113). The fragmentation is also explained (Page No. 114).

All the products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs.

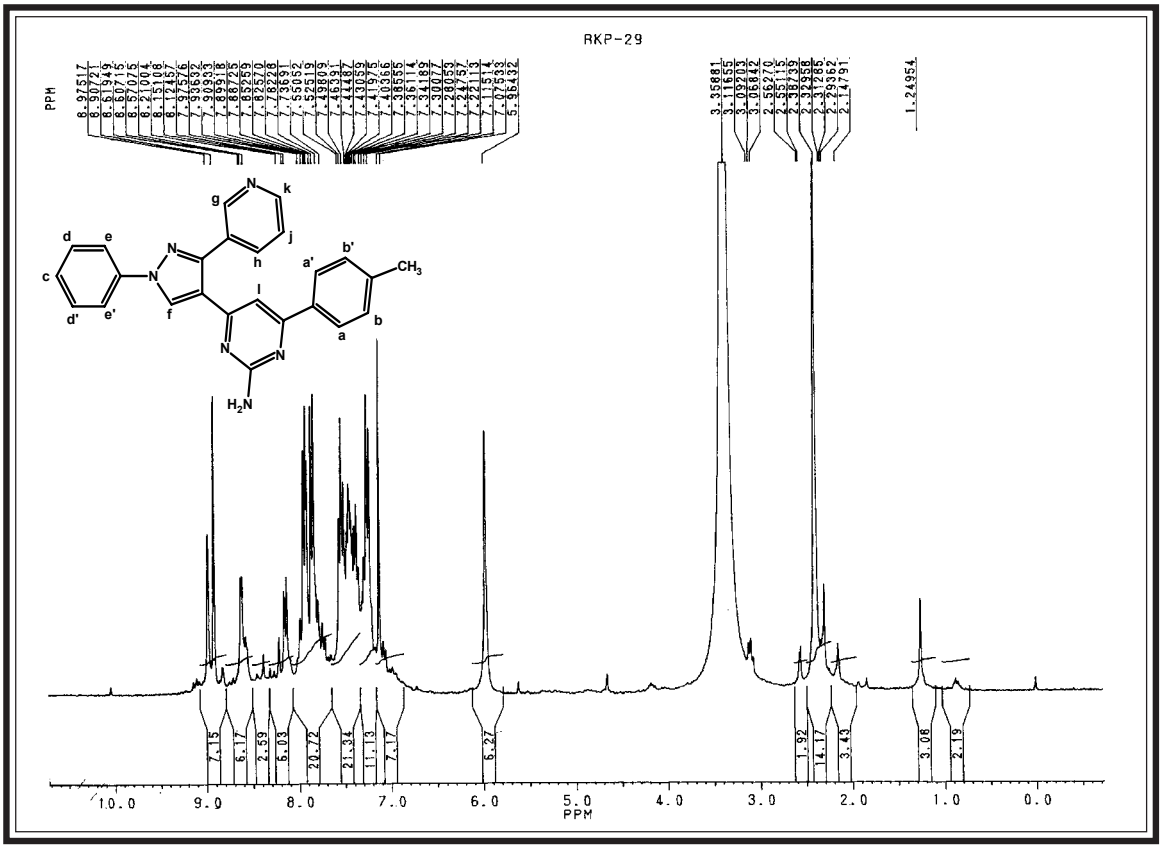
IR SPECTRAL STUDY OF 2-AMINO-4-(p-ANISYL)-6-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOLE-4-YL]PYRIMIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2918	2975-2950	95
-CH_3	C-H str. (sym.)	2850	2880-2860	,,
	C-H i.p.def. (asym.)	1448	1470-1435	,,
	C-H o.o.p.def. (sym.)	1375	1390-1370	,,
Aromatic	C-H str.	3053	3090-3030	96
	C=C str.	1498	1540-1480	,,
	C-H o.o.p. (def)	815	835-810	,,
Pyrazole	C=N str.	1629	1600-1650	,,
moiety	C-N str.	1226	1230-1020	,,
Primary amine	N=H str.	3298	3559-3350	95
Pyrimidine	C=N str.	1546	1580-1520	96
	C-N str.	1226	1350-1200	
		Overlapped		

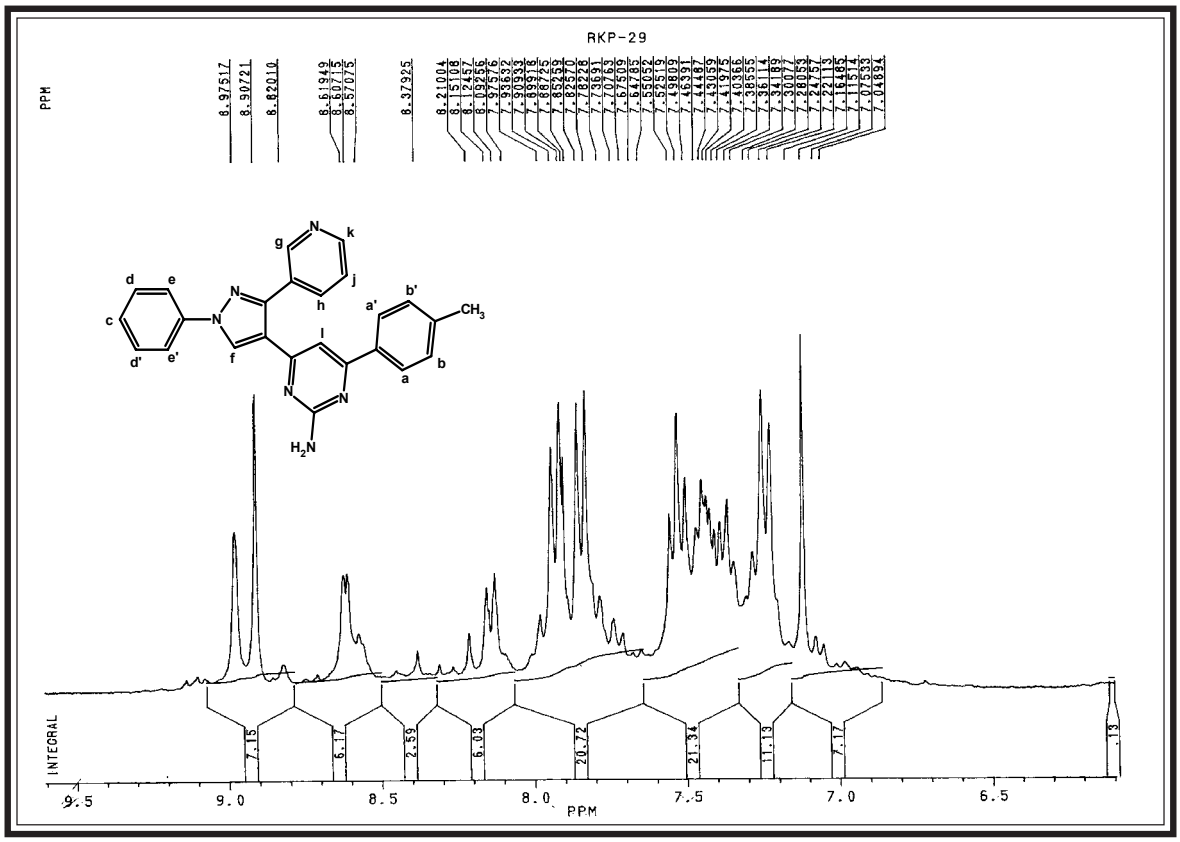
PMR SPECTRAL STUDY OF 2-AMINO-4-(p-TOLYL)-6-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOLE-4'-YL]PYRIMIDINE

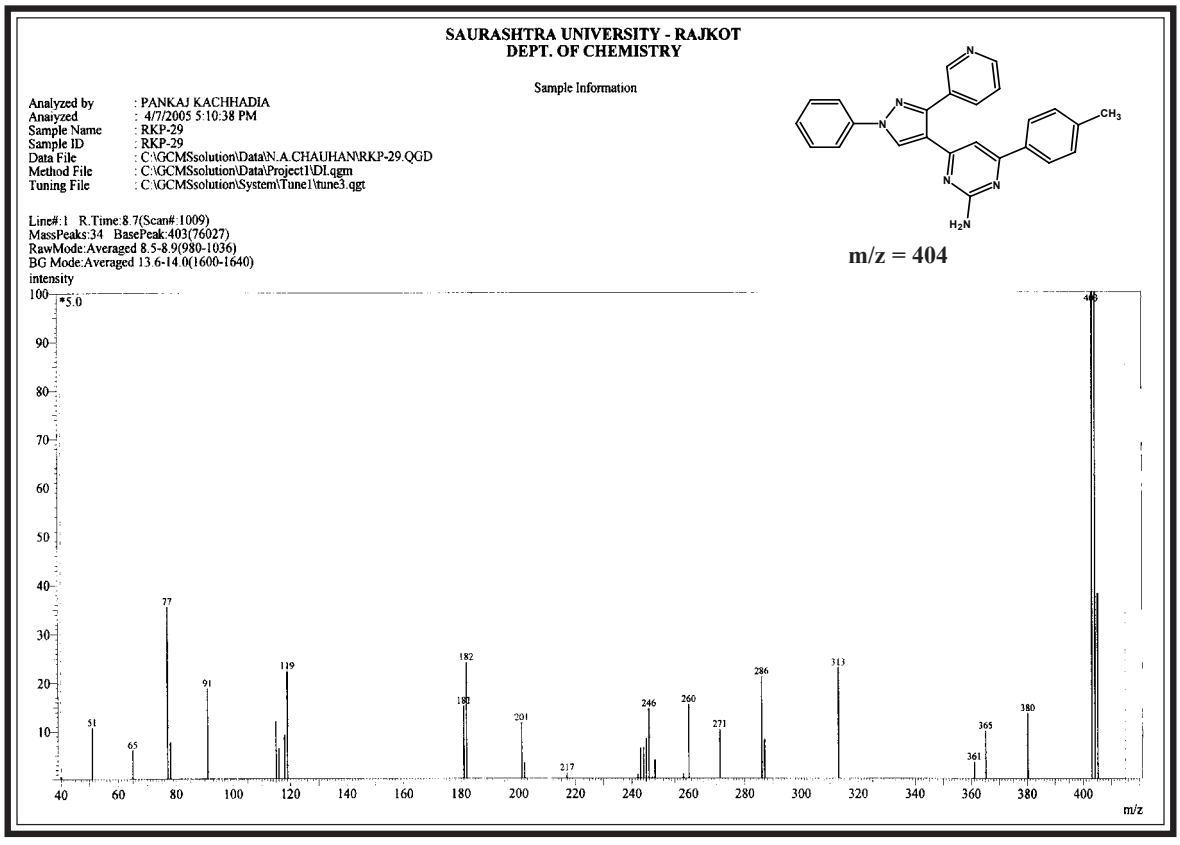


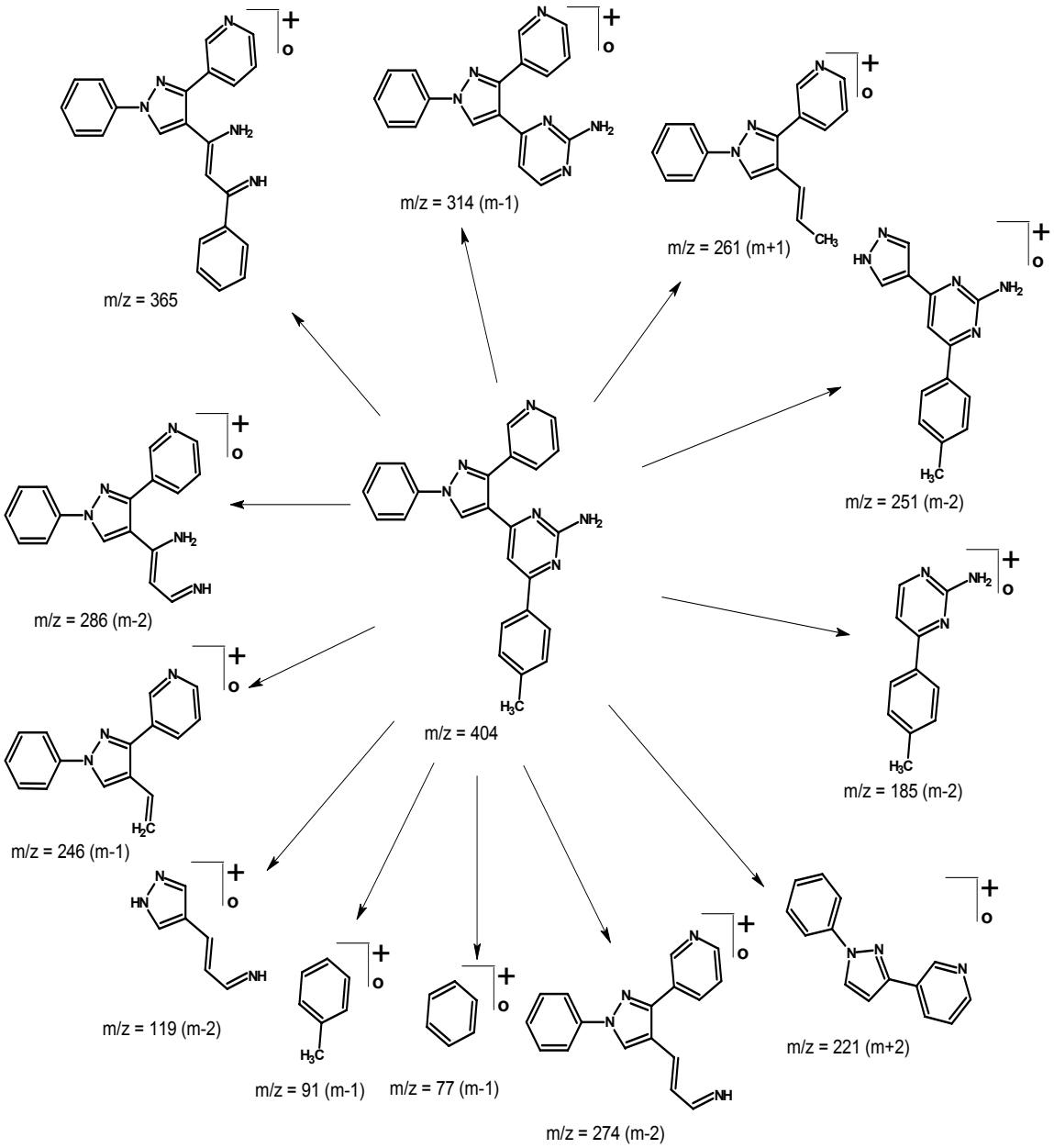
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.38	3H	singlet	Ar-CH_3	-
2	5.96	2H	singlet	-NH_2	-
3	7.22-7.25	2H	doublet	Ar-Hb,b'	Jbb'=7.9
4	7.34-7.43	1H	multiplet	Ar-Hh	-
5	7.49-7.55	3H	multiplet	Ar-Hc,d,d'	-
6	7.82-7.85	2H	doublet	Ar-Ha,a'	Jaa'=8.1
7	7.90-7.93	2H	doublet	Ar-He,e'	Jee'=8.1
8	8.12-8.21	2H	multiplet	Ar-Hj,i	-
9	8.57-8.62	1H	multiplet	Ar-Hk	-
10	8.90	1H	singlet	Ar-Hf	-
11	8.97	1H	singlet	Ar-Hg	-

EXPANDED AROMATIC REGION






m/z = 365
m/z = 314 (m-1)
m/z = 261 (m+1)
m/z = 251 (m-2)
m/z = 286 (m-2)
m/z = 404
m/z = 185 (m-2)
m/z = 246 (m-1)
m/z = 119 (m-2)
m/z = 91 (m-1)
m/z = 77 (m-1)
m/z = 274 (m-2)
m/z = 221 (m+2)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-4-ARYL-6-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOLE-4'-YL]PYRIMIDINES

[A] Synthesis of 1,N-Phenyl-3-â-pyridyl-4-formyl pyrazole

See Part-I, Section-I (B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-II (B).

[C] Synthesis of 2-Amino-4-(p-Tolyl)-6-(1',N-phenyl-3'-â-pyridyl-1,H-pyrazole-4'-yl)pyrimidine

A mixture of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one (3.65 g, 0.01 M) and guanidine hydrochloride (1.10 g, 0.01M) was refluxed in ethanol on a water bath for 4-5 hrs. The reaction mixture was poured in to crushed ice. The product was filtered and crystallized from ethanol. Yield 47%, m.p. 256°C. Anal. Calcd. for $C_{25}H_{20}N_6$; Required: C, 74.24; H, 4.98; N, 20.78 %; Found: C, 74.19; H, 4.95; N, 20.76%.

Similarly other 2-Amino-4-aryl-6-(1',N-phenyl-3'-â-pyridyl-1,H- pyrazole-4'-yl) pyrimidines were prepared. The physical data are recorded in Table No. 7.

[D] Antimicrobial activity of 2-Amino-4-aryl-6-(1',N-phenyl-3'-â-pyridyl-1,H-pyrazole-4'-yl)pyrimidines

Antimicrobial testing were carried out as described in Part-I Section-II (C). The zones of inhibition of test solution are recorded in Graphical Chart No.7.

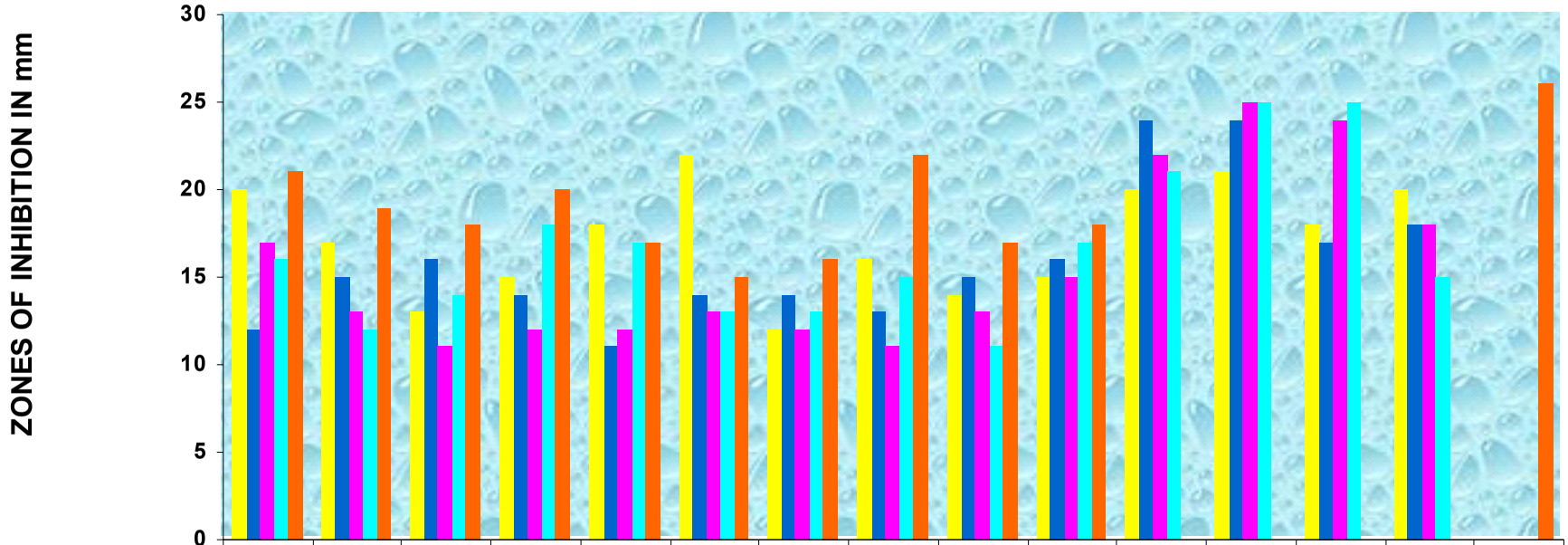
TABLE NO. 7 : PHYSICAL CONSTANTS OF 2-AMINO-4-ARYL-6-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOLE-4'-YL)PYRIMIDINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
7a	4-CH_3-C_6H_4-	$C_{25}H_{20}N_6$	404	256	0.56	47	20.78	20.76
7b	4-OCH_3-C_6H_4-	$C_{25}H_{20}N_6O$	420	243	0.63	39	19.99	19.97
7c	2-OH-C_6H_4-	$C_{24}H_{18}N_6O$	406	210	0.48	45	20.68	20.65
7d	4-OH-C_6H_4-	$C_{24}H_{18}N_6O$	406	223	0.51	51	20.68	20.66
7e	4-Cl-C_6H_4-	$C_{24}H_{17}ClN_6$	424.5	269	0.60	63	19.78	19.77
7f	4-F-C_6H_4-	$C_{24}H_{17}FN_6$	408	237	0.42	57	20.58	20.56
7g	4-Br-C_6H_4-	$C_{24}H_{17}BrN_6$	469	226	0.49	52	17.91	17.89
7h	3-NO_2-C_6H_4-	$C_{24}H_{17}N_7O_2$	435	250	0.32	37	22.52	22.49
7i	4-NO_2-C_6H_4-	$C_{24}H_{17}N_7O_2$	435	265	0.38	43	22.52	22.51
7j	4-NH_2-C_6H_4-	$C_{24}H_{19}N_7$	405	192	0.50	49	24.18	24.16

*TLC Solvent System : Acetone : Benzene

3 : 7

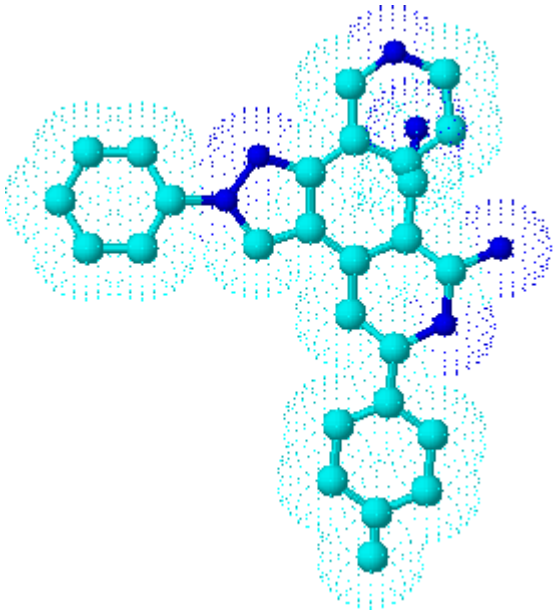
GRAPHICAL CHART NO. 7 : ANTIMICROBIAL ACTIVITY OF 2-AMINO-4-ARYL-6-(1',N-PHENYL-3'-â-PYRIDYL -1,H-PYRAZOLE-4'-YL)PYRIMIDINES



	7a	7b	7c	7d	7e	7f	7g	7h	7l	7j	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	20	17	13	15	18	22	12	16	14	15	20	21	18	20	0
B. subtillus	12	15	16	14	11	14	14	13	15	16	24	24	17	18	0
E.coli	17	13	11	12	12	13	12	11	13	15	22	25	24	18	0
P. vulgaris	16	12	14	18	17	13	13	15	11	17	21	25	25	15	0
A. niger	21	19	18	20	17	15	16	22	17	18	0	0	0	0	26

BIOLOGICAL EVALUATION OF 2-AMINO-4-ARYL-6-(1',N-PHENYL-3'-â-PYRIDYL-1,H-PYRAZOLE-4'-YL)PYRIMIDINES

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
7f(22)	7c(16)	7a(17)	7d(18)	7h(22)
7a(20)	7j(16)		7e(17)	7a(21)
7e(18)			7j(17)	7d(20)
7f(17)			7a(16)	7b(19)
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	



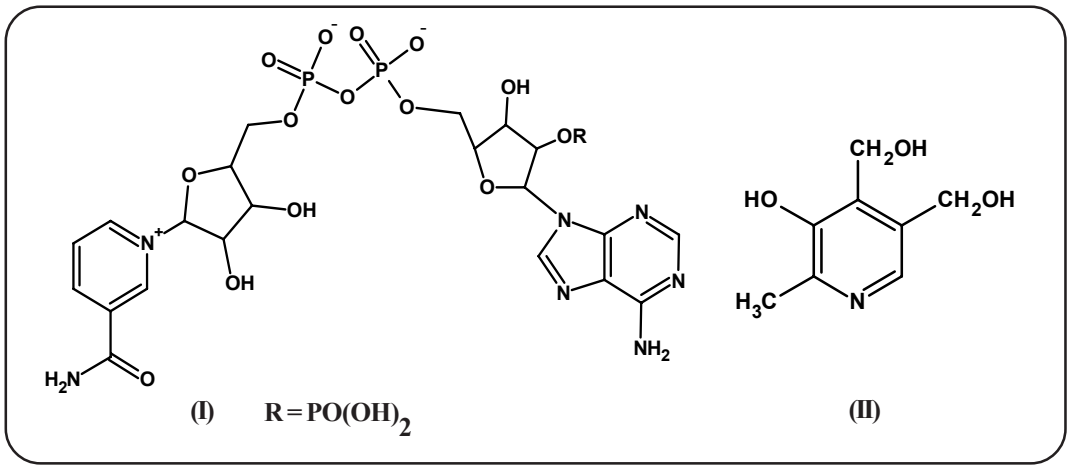
PART - VI

STUDIES ON

CYANOPYRIDINES

INTRODUCTION

Historically, a wide range of biological activities have been attributed to pyridine derivatives. Pyridine-3-carboxamide occurs as a component of the structure of the important coenzymes NADP + (I), one of the B2 complex of vitamins, occurs in red blood carpuscles and participates in biochemical redox reaction. Pyridoxal (Vitamin B6) (II), occurs in yeast and wheatgerm is an important food additive.

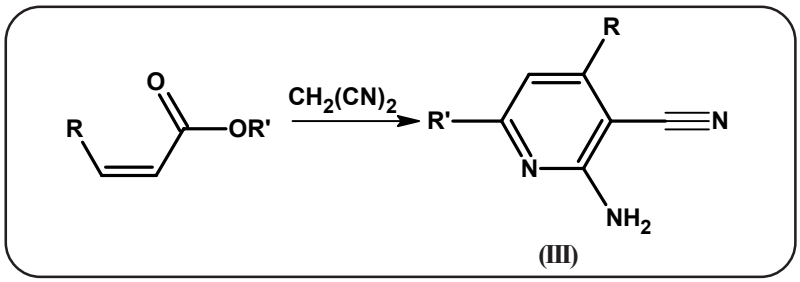


The availability of 3-cyanopyridine, nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

SYNTHETIC ASPECT

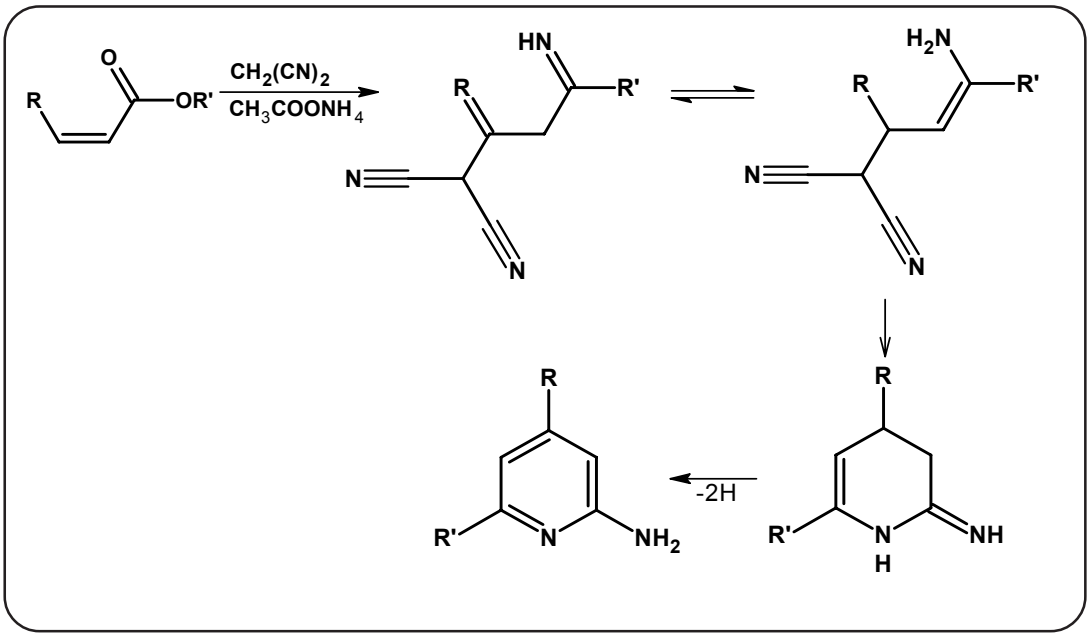
Different methods for the preparation of 3-cyanopyridines are available in literature[298-304].

Sakurai and Midorikwa[305,306] have reported that malononitrile reacts with a,bunsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines (III).



MECHANISM:

The reaction proceeds through conjugated addition of active methylene compounds to the a,bunsaturated system as shown below.

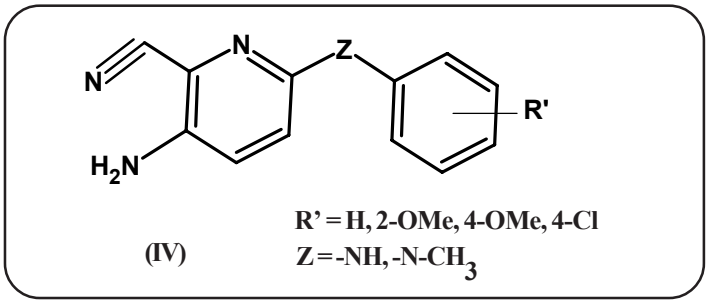


THERAPEUTIC IMPORTANCE

The cyanopyridine derivatives are extensively used in medicine, due to its antidiabetic, antihypertensive, anticholestemic, antifungal and antibacterial properties. Various cyanopyridines are known to exhibit a broad spectrum of biological activities such as,

1. Anti HIV[307]
2. Antitubercular[308]
3. Analgesic[309]
4. Insecticidal[310]
5. Antisoriasis[311]
6. Antihypertensive[312]
7. Antifungal[313]
8. Antiepileptic[314]
9. Anticonvulsant[315]
10. Antibacterial[316,317]
11. Antiinflammatory[318]

Gangjee et. al.[319] have synthesised some novel cyanopyridine derivatives of type-(IV) as potent antitumor agents.

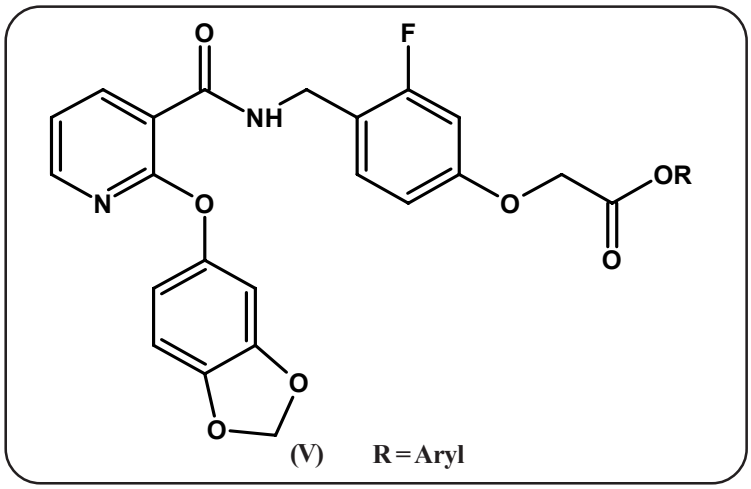


(IV)

The insecticidal activity of cyanopyridines has been screened by Y. Sasaki et. al.[320] Umed Ten et. al.[321] have prepared cyanopyridines as agrochemical fungicides. The oxide activator bleaching activity of cyanopyridine has been proved by Rees M.[322] Oshida Mario[323] prepared cyanopyridine derivatives which inhibit cerebral edema and delayed neuron death. Hence, they are useful as cerebral edema inhibitors as cerebrovascular disorder remedies.

Several co-workers have prepared some novel cyanopyridine derivatives and reported their cholinesterase inhibitors[324], antihistaminic and antiallergic[325], adernegic[326], herbicidal[327], antiinflammatory[328], and insecticidal[329] activities.

Chambers et al.[330] have synthesised new carbonyl substituted pyridine derivatives (V) and prooved that they are inhibitors of phosphodiestercy (IV) isozymes.



(V) R = Aryl

Some new 3-cyanopyridine derivatives have been prepared by Hammama A. and co-workers[331] showing anticancer and anti HIV-I activity.

Abdallah N. et. al.[332] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity. Ladouceur Getan H. et. al.[333] have synthesised some new pyridine derivatives behaving as glucagon antagonist. Caroline Charlie and co-worker[334] have prepared pyridine derivatives having antiinflammatory activity. Antimicrobial activity of 3-cyanopyridine derivatives have been studied by Mona Komel et. al.[335]

CONTRIBUTION FROM OUR LABORATORY

H. H. Parekh et. al.[336-337] have synthesised the series of cyanopyridines and postulated them as antimicrobial agents. A. R. Parikh et. al.[338] have prepared some new cyanopyridines and studied their antimicrobial activity. H. H. Parekh et. al.[339]have synthesised 3-cyanopyridines bearing quinoline nucleus and tested their antimicrobial and antitubercular activity.

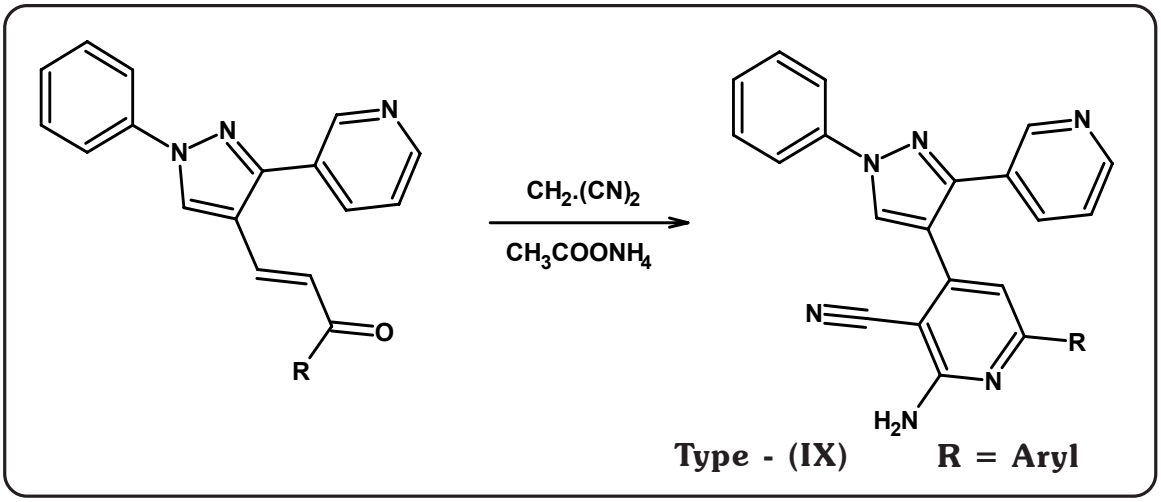
In view of the above observations, the synthesis of new 3-cyanopyridine derivatives bearing 1N-Phenyl-3-β-pyridyl-4-formyl pyrazol moiety, were aimed at investigating biological activities of these compounds.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-6-ARYL PYRIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-6-ARYL PYRIDINES

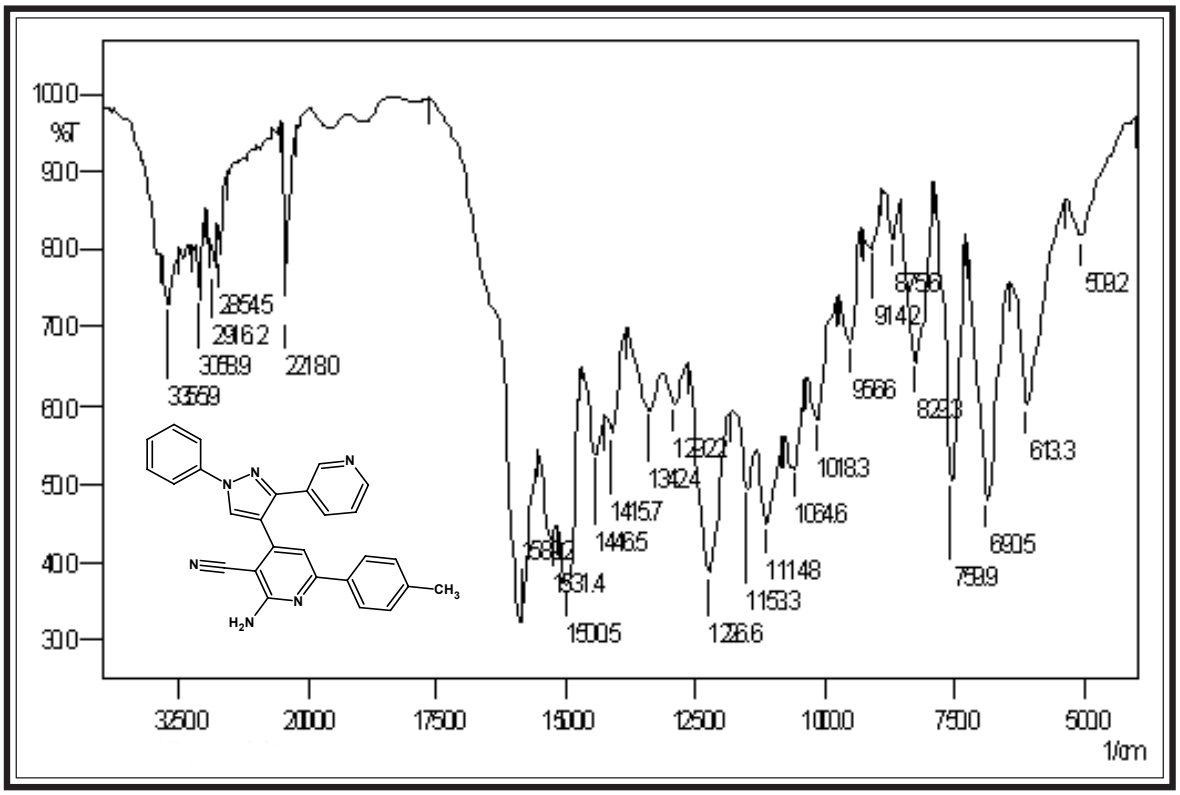
In the past years, considerable evidence has been accumulated to demonstrate the efficiency of cyanopyridines. To further assess the potential of such a class of compounds cyanopyridine derivatives of type (IX) have been synthesised by condensation of malononitrile and ammonium acetate with 1-aryl-3-(1',N-phenyl-3'-β-pyridyl-pyrazol-4'- yl)-2-propen-1-ones.



The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. The mass spectra of 2-amino-3-cyano-4-[1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl]-6-(p-tolyl) pyridines give m/z = 428 (recorded on Page No. 126). The fragmentation is also explained (Page No. 127).

The products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activity of synthesised compounds were compared with standard drugs.

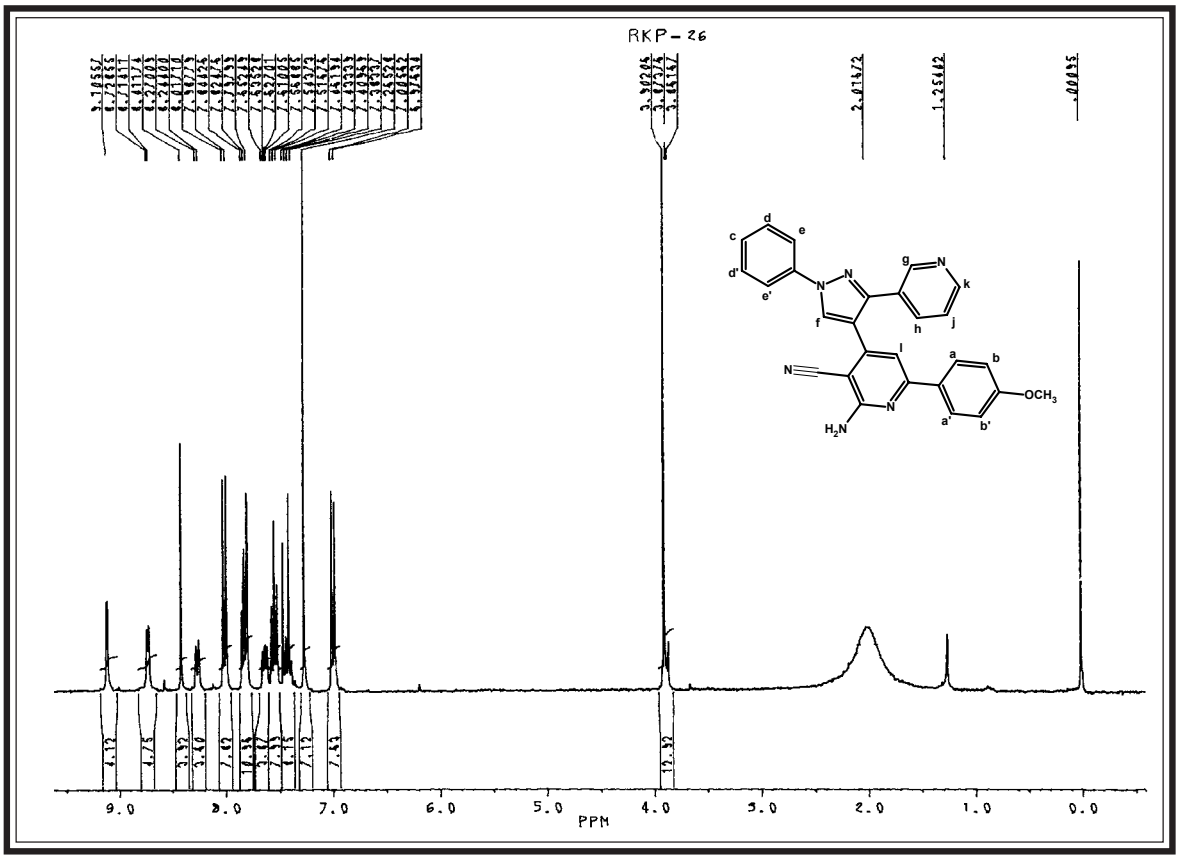
IR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-6-(p-TOLYL) PYRIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2916	2995–2920	95
$-CH_3$	C – H str. (sym.)	2854	2880–2850	"
	C – H i.p. (def.)	1446	1470–1435	"
	C – H o.o.p. (def.)	1342	1385–1330	"
Aromatic	C – H str.	3058	3080–3010	96
	C – H i.p. (def.)	1018	1110–1000	"
	C – H o.o.p (def.)	829	835–810	"
Pyrazole	C = N str.	1589	1650–1600	96
moiety	C = C str.	1531	1585–1480	"
	C – N str.	1292	1350–1200	"
Pyridine	C = C str.	1589 Overlapped	1650-1520	95
	N- H str.	3354	1075–1020	"
	N- H def.	1589	1075–1020	"
	C ≡ N str.	2218	2240-2210	"

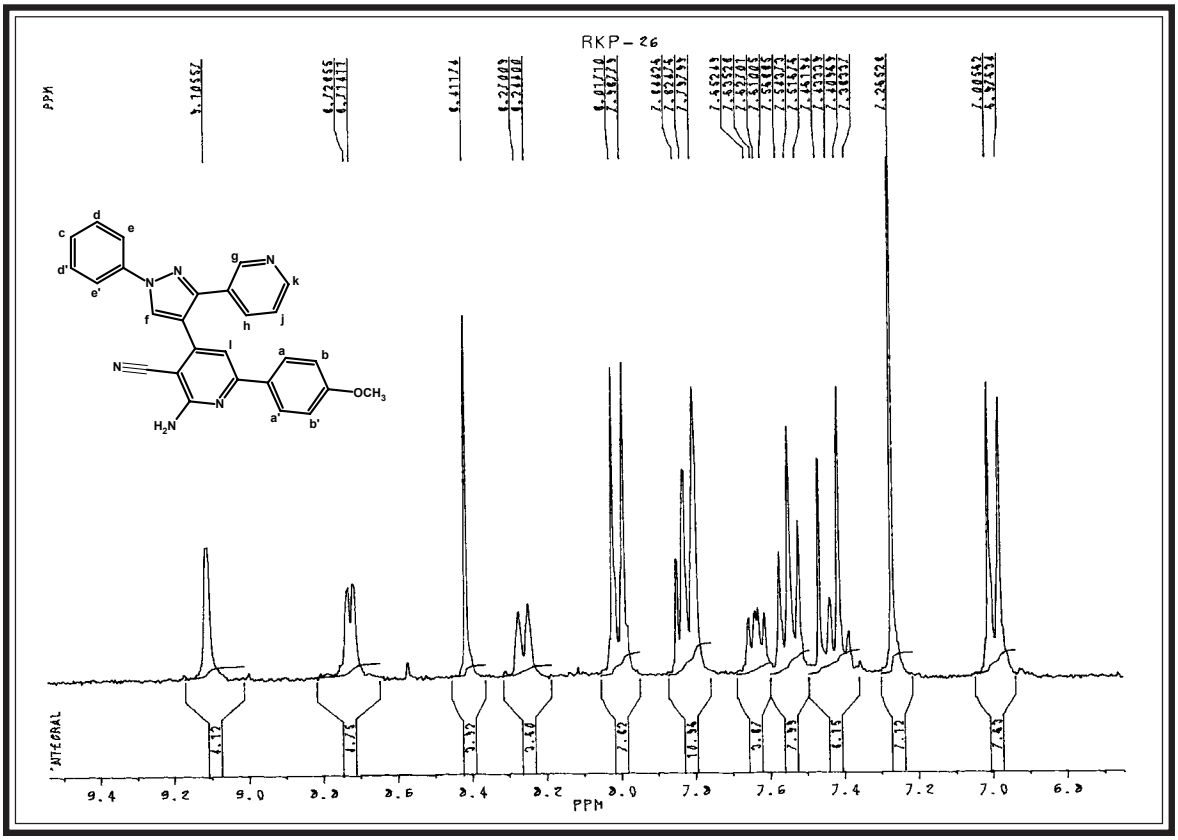
PMR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-6-(p-ANISYL) PYRIDINE

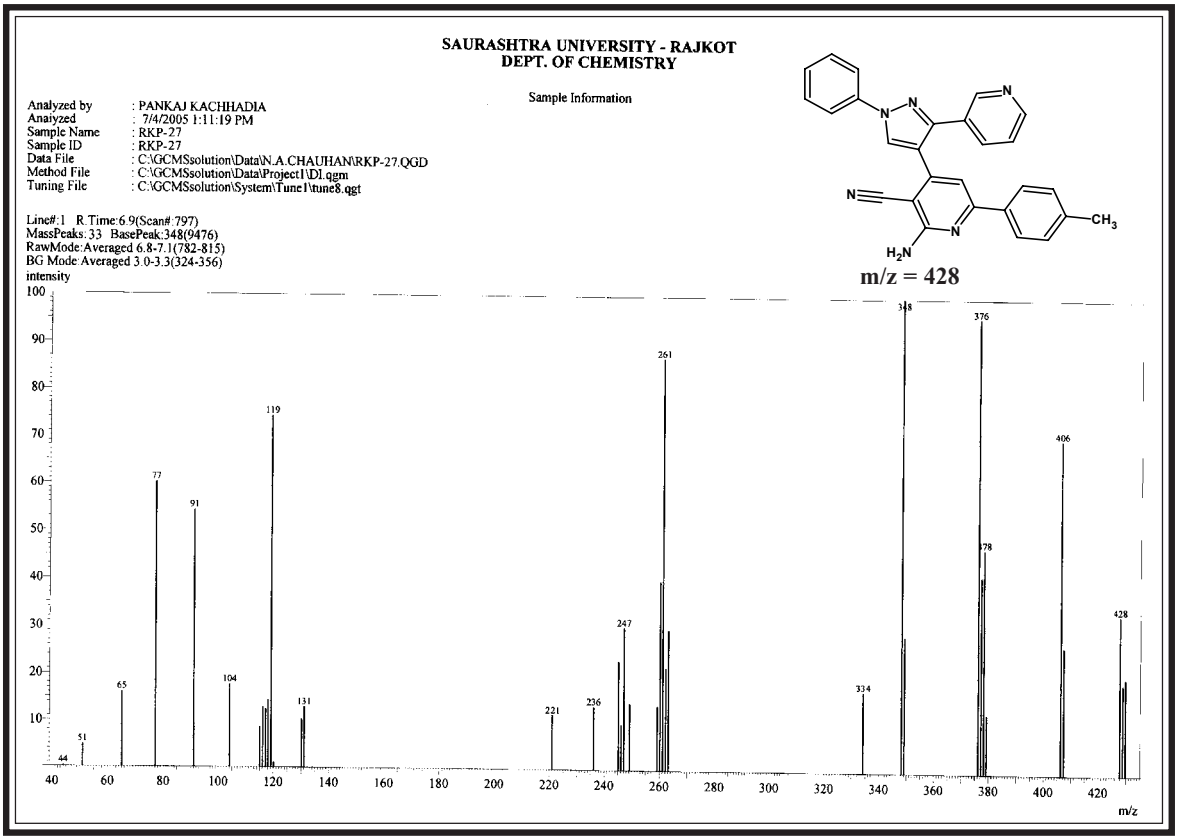


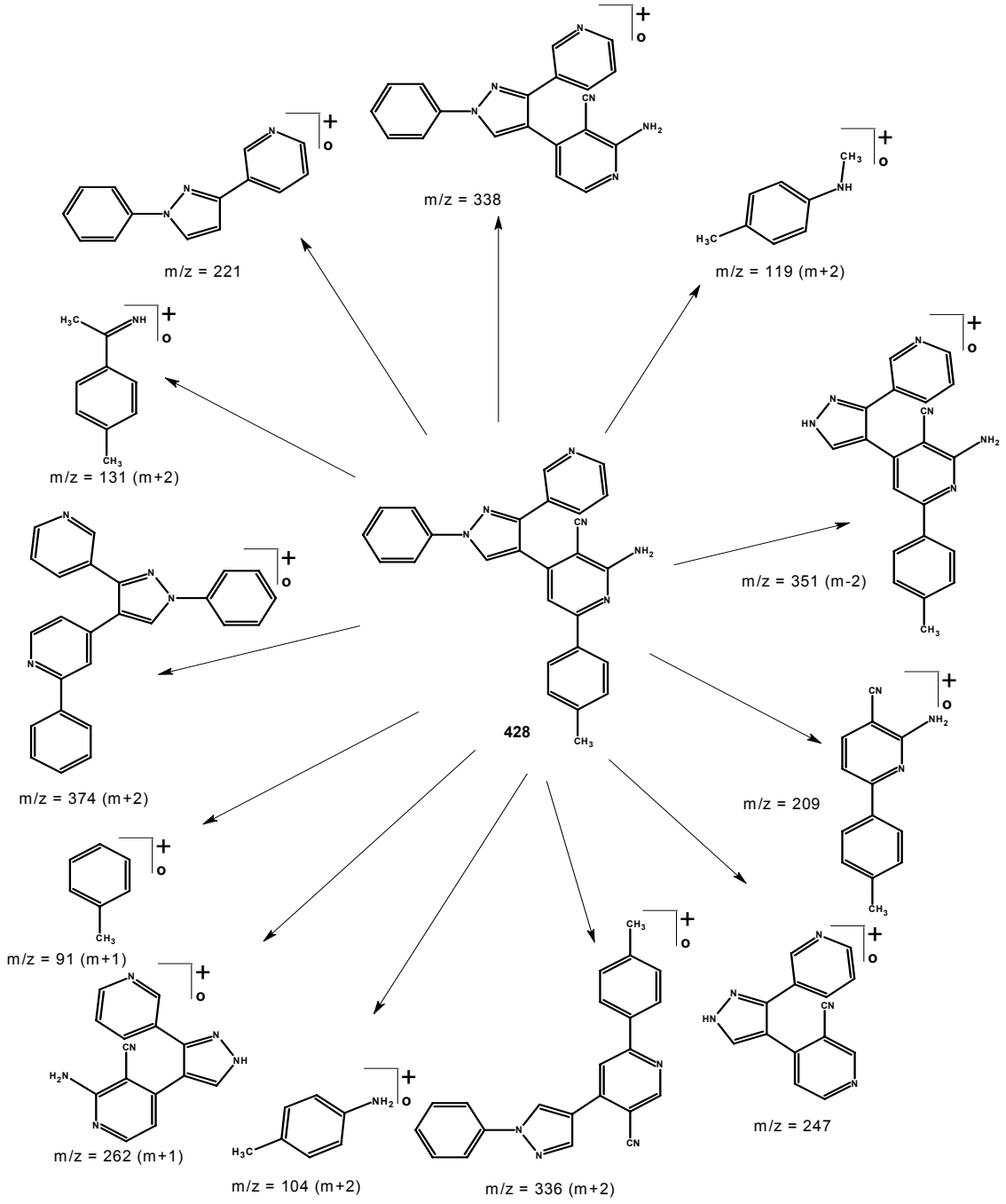
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.9	3H	singlet	Ar-OCH_3	-
2	6.97-7.0	2H	doublet	Ar-Haa'	Jaa'=8.8
3	7.40	1H	singlet	Ar-Hl	-
4	7.51-7.54	2H	doublet	Ar-Hbb'	Jbb'=8.1
5	7.61-7.65	1H	multiplet	Ar-Hh	-
6	7.79-7.84	2H	doublet	Ar-Hdd'	Jdd'=8.0
		1H	multiplet	Ar-Hc	-
7	7.98-8.01	2H	doublet	Ar-Hee'	Jee'=8.8
8	8.24-8.27	1H	doublet	Ar-Hjk	Jjk=7.8
9	8.41	1H	singlet	Ar-Hf	-
10	8.71-8.73	1H	doublet	Ar-Hk	Jkj=6.00
11	9.1	1H	singlet	Ar-Hg	-

EXPANDED AROMATIC REGION






m/z = 221
m/z = 338
m/z = 119 (m+2)
m/z = 131 (m+2)
m/z = 351 (m-2)
428
m/z = 374 (m+2)
m/z = 209
m/z = 91 (m+1)
m/z = 262 (m+1)
m/z = 104 (m+2)
m/z = 336 (m+2)
m/z = 247

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-6-ARYL PYRIDINES

[A] Synthesis of 1,N-Phenyl-3-â-pyridyl-4-formyl pyrazole

See Part-I, Section-I (B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one

See Part-I, Section-II (B).

[C] Synthesis of 2-Amino-3-cyano-4-[1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl]-6-(p-tolyl) pyridine

A mixture of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one (3.65 g, 0.01 M), malononitrile (0.66 g, 0.01 M) and ammonium acetate (6.61g, 0.08M) dissolved in absoulte alcohol was refluxed for 10 hrs. at to m.p. 60-70^{o}C. The reaction product was poured into ice, crude product was isolated, crystallised from ethanol. Yield 65%, m.p. 230^{o}C ($C_{27}H_{20}N_6$; Found : C, 75.59%; H, 4.65%; N, 19.58%; Requires : C, 75.68%; H, 4.70%; N, 19.61%).

Similarly other cyanopyridines have been obtained. The physical data are recorded in Table No. 8.

[D] Antimicrobial activity of 2-Amino-3-cyano-4-[1',N-phenyl-3'-â-pyridyl- pyrazol-4'-yl]-6-aryl pyridines

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solutions are recorded in Graphical Chart No.8.

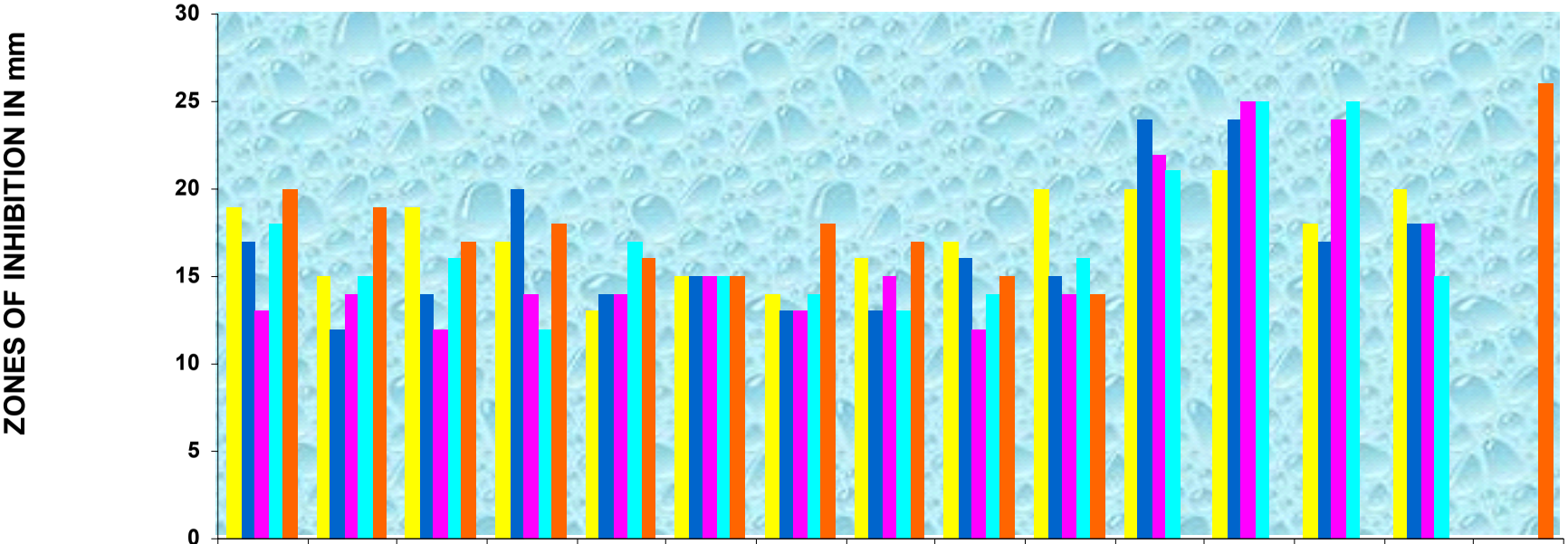
TABLE NO. 8 : PHYSICAL CONSTANTS OF 2-AMINO-3-CYANO-4-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-6-ARYL PYRIDINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
8a	4-CH_3-C_6H_4-	$C_{27}H_{20}N_6$	428	230	0.62	47	19.61	19.58
8b	4-OCH_3-C_6H_4-	$C_{27}H_{20}N_6O$	444	219	0.57	52	18.91	18.88
8c	2-OH-C_6H_4-	$C_{26}H_{18}N_6O$	430	243	0.53	62	19.52	19.50
8d	4-OH-C_6H_4-	$C_{26}H_{18}N_6O$	430	237	0.49	56	19.52	19.49
8e	4-Cl-C_6H_4-	$C_{26}H_{17}ClN_6$	448.5	262	0.37	59	18.72	18.68
8f	4-F-C_6H_4-	$C_{26}H_{17}FN_6$	432	218	0.45	42	19.43	19.40
8g	4-Br-C_6H_4-	$C_{26}H_{17}BrN_6$	493	240	0.59	58	17.03	17.01
8h	3-NO_2-C_6H_4-	$C_{26}H_{17}N_7O_2$	459	198	0.50	43	21.34	21.31
8i	4-NO_2-C_6H_4-	$C_{26}H_{17}N_7O_2$	459	217	0.43	45	21.34	21.30
8j	4-NH_2-C_6H_4-	$C_{26}H_{19}N_7$	429	265	0.69	51	22.83	22.80

*TLC Solvent System : Acetone : Benzene

3 : 7

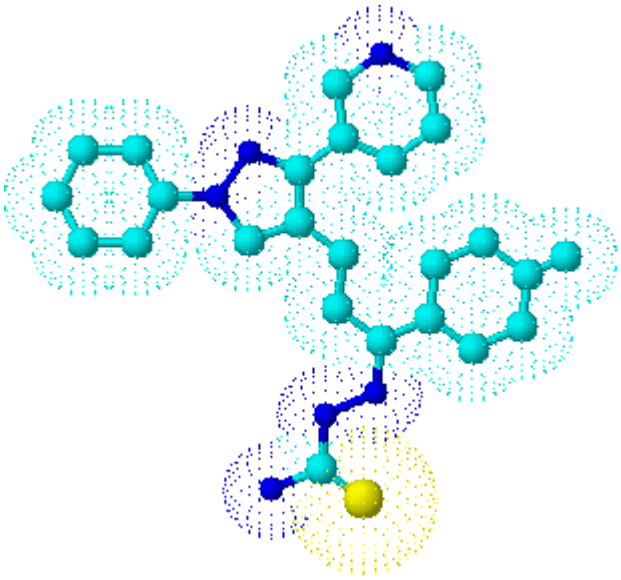
GRAPHICAL CHART NO. 8 : ANTIMICROBIAL ACTIVITY OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-6-ARYL PYRIDINES



	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	19	15	19	17	13	15	14	16	17	20	20	21	18	20	0
B. subtillus	17	12	14	20	14	15	13	13	16	15	24	24	17	18	0
E.coli	13	14	12	14	14	15	13	15	12	14	22	25	24	18	0
P. vulgaris	18	15	16	12	17	15	14	13	14	16	21	25	25	15	0
A. niger	20	19	17	18	16	15	18	17	15	14	0	0	0	0	26

BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL]-6-ARYL PYRIDINES

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
8j(20)	8d(20)	8a(18)	8a(18)	8a(20)
8a(19)	8a(17)		8e(17)	8b(19)
8c(19)			8c(16)	8d(18)
			8j(16)	8g(18)
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	



PART - VII

STUDIES ON

THIOSEMICARBAZONES

INTRODUCTION

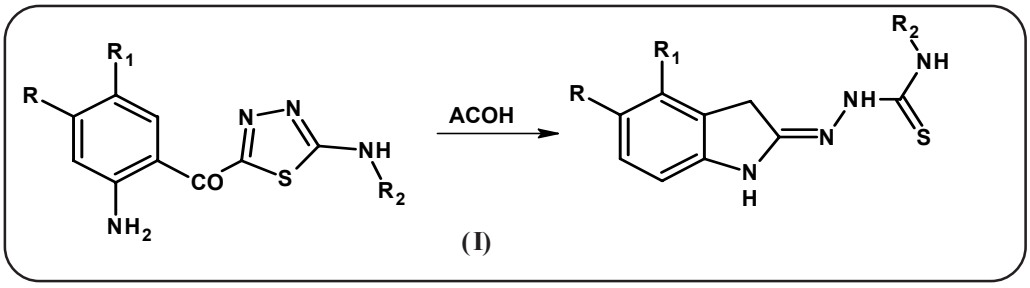
*T*hiosemicarbazones, also known as amino derivatives of thiourea, have found their way into almost every branch of chemistry, commercially they are used as dyes, photographic films, plastic and in textiles industry. Thiosemicarbazones are extensively used in medicinal chemistry.

SYNTHETIC ASPECT

The reaction between thiosemicarbazide and carbonyl compound have aroused a great attention because of the interesting nature of resulting compounds for their uses in medicine.

Different methods for the synthesis of thiosemicarbazones are available in literature.[340-343]

1. A. B. Tomchin[344] has synthesised thiosemicarbazones by the recyclisation of 2-amino-5-(2-aminoaroyl)-1,3,4-thiadiazoles.



(I)

2. A. K. Bhatt and co-workers[345] have synthesised thiosemicarbazones by the condensation of chalcones with thiosemicarbazide.

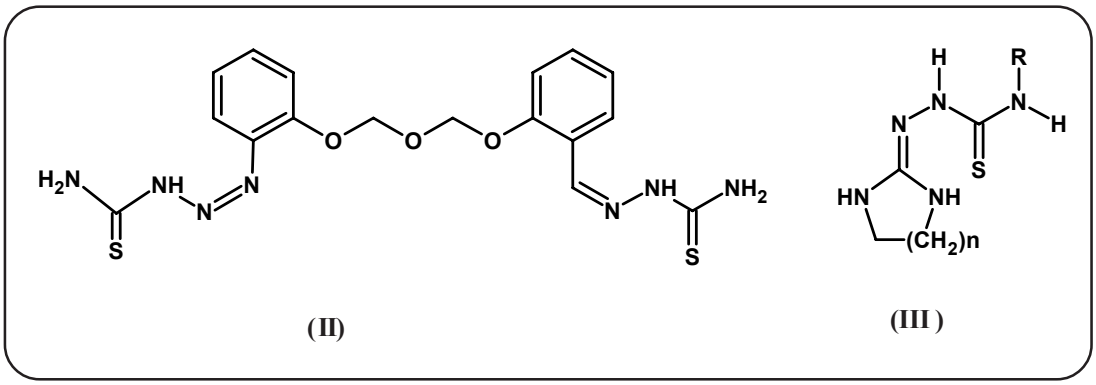
THERAPEUTIC IMPORTANCE

Thiosemicarbazones exhibit a wide range of physiological and biological activities such as,

1. Anticancer[346,347]
2. Anticonvulsant[348]
3. Antiherpes[349]
4. Antimalarial[350]
5. Antirheumatics[351]
6. Antifungal[352,353]
7. Antibacterial[354]
8. Antidiabetic[355]
9. Antitumor[356,357]
10. Anthelmintics[358]

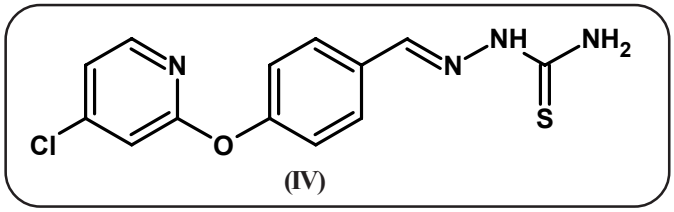
Kalyan C. N. and co-workers[359] have synthesised 1-(p-benzoylamino)-benzoyl-4-substituted thiosemicarbazone derivatives and screened for their antimicrobial activity. Siatra T. and co-workers[360] have prepared some new thiosemicarbazones from 3-acetyl indole and reported their effect on DNA synthesis and cell proliferation.

Li Jun et. al.[361] has preped some new 3-amino pyrimidine-2-carboxaldehyde thiosemicarbazone derivatives and reported them as novel prodrug forms of ribonucleotide reductase inhibitors. Fedorova O. V. and coworkers[362]have synthesised some new thiosemicarbazones (II) exhibiting good *in vitro* tuberculostatic activity. Anticancer activity of thiosemicarbazone derivatives (III) have been reported by Krezel Izabella.[363]



(II) **(III)**

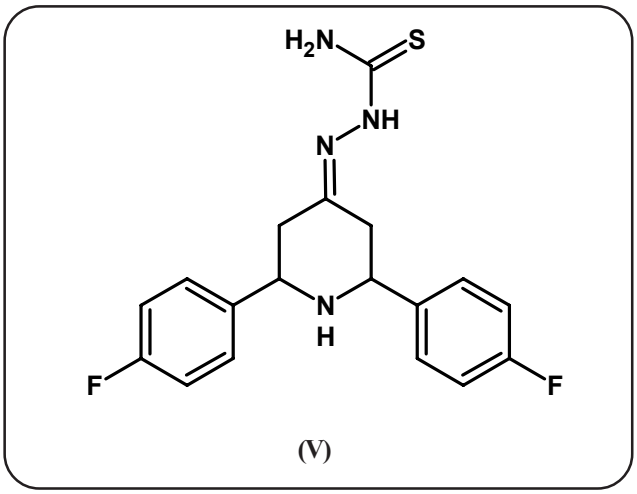
W. Deteng and co-workers[364] have prepared thiosemicarbazones (IV) and documented their usefulness as sodium channel blockers.



(IV)

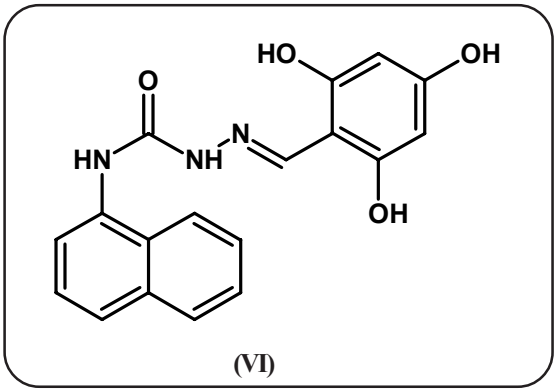
Magalhaes N. et. al.[365] have synthesised some new thiosemicarbazones and reported their anticancer activity. Toxicity and fungiocity of some novel thiophene-2-carboxaldehyde thiosemicarbazones have been evaluated by Teoh-Siang-Guan et. al.[366] Antitumor activity of thiosemicarbazones was documented by Dulanyan E. R. and co-workers.[367]

Rajasekaran A. and co-workers[368] have prepared some new thiosemicarbazone (V) and reported their antimicrobial activity.



(V)

Duffy K. J.[369] prepared some new thiosemicarbazones (VI) and reported them as thrombopoietin mimetics.



(VI)

Thus the important role displayed by thiosemicarbazones for various physiological activities prompted us to prepare a series of thiosemicarbazones having pyrazole nucleus as parent molecule which has been described as under.

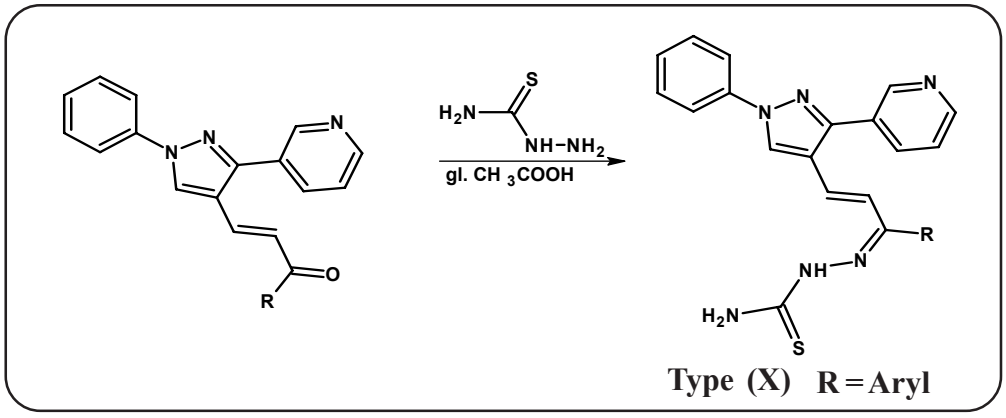
SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONES

SECTION-II : MICROWAVE INDUCED AN EXPENDITOUS SYNTHESIS OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONES

SECTION -I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONES

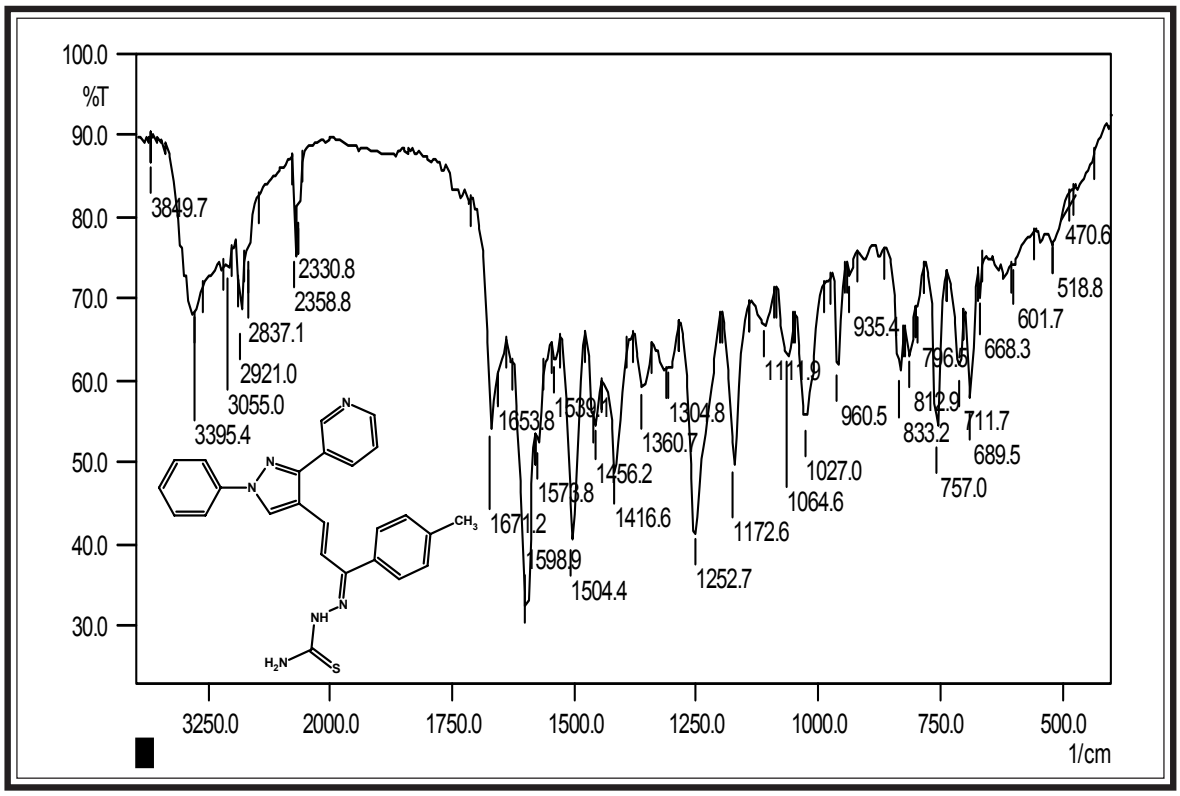
In the past years, considerable evidence has been accumulated to demonstrate the efficiency of thiosemicarbazones. To further assess the potential of such a class of compounds, thiosemicarbazones of type (X) have been prepared by the condensation of 1-aryl-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-ones with thiosemicarbazide.



The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. The mass spectra of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-thiosemicarbazonegive m/z = 438 (recorded on Page No. 138). The fragmentation is also explained (Page No. 139).

The products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

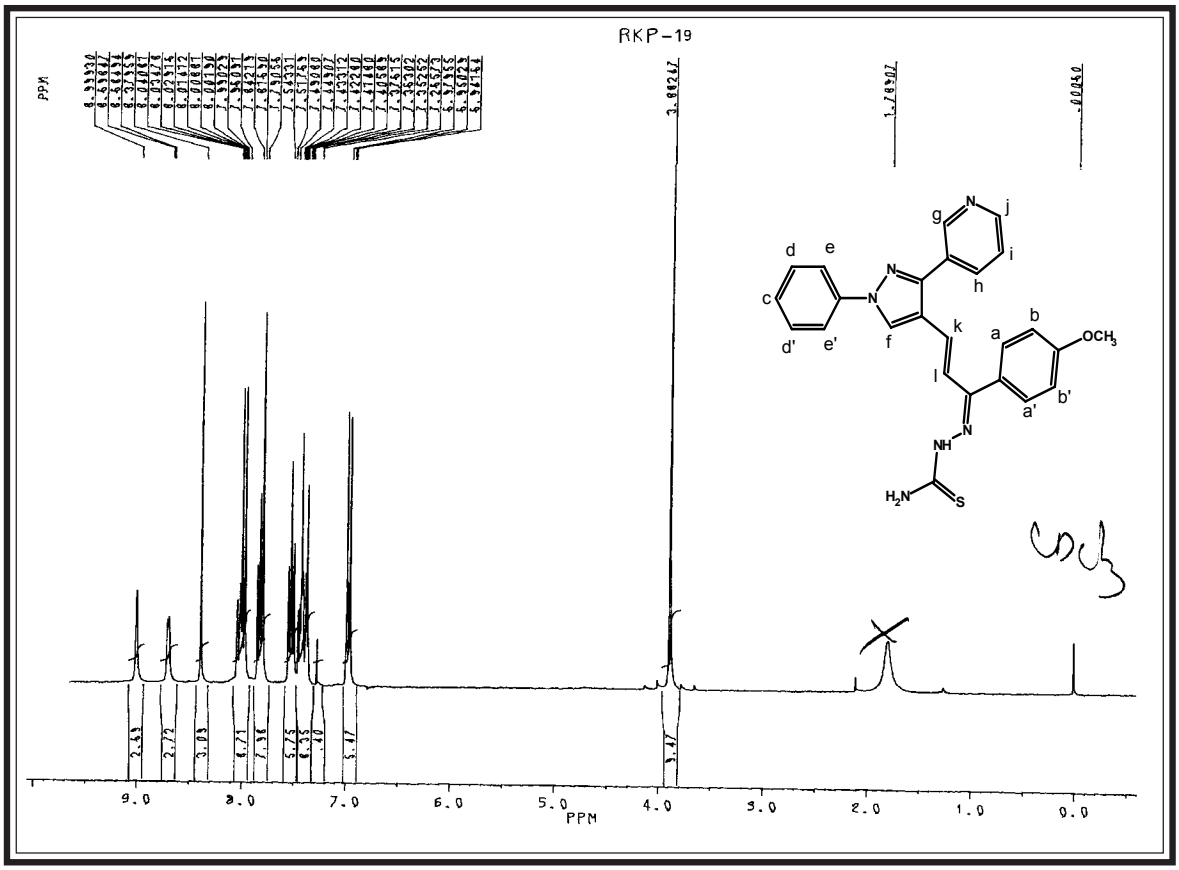
IR SPECTRAL STUDY OF 1-(p-TOLYL)-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2921	2995–2920	95
$-CH_3$	C – H str. (sym.)	2837	2880–2850	"
	C – H i.p. (def.)	1416	1470–1435	"
	C – H o.o.p. (def.)	1360	1385–1330	"
Aromatic	C – H str.	3055	3080–3010	96
	C – H i.p. (def.)	1172	1110–1000	"
	C – H o.o.p (def.)	812	835–810	"
Pyrazole	C = N str.	1598	1650–1600	96
moiety	C – N str.	1252	1350–1200	"
Amine	N- H str.	3395	1075–1020	"
	C= N str.	1598	1660-1580	"

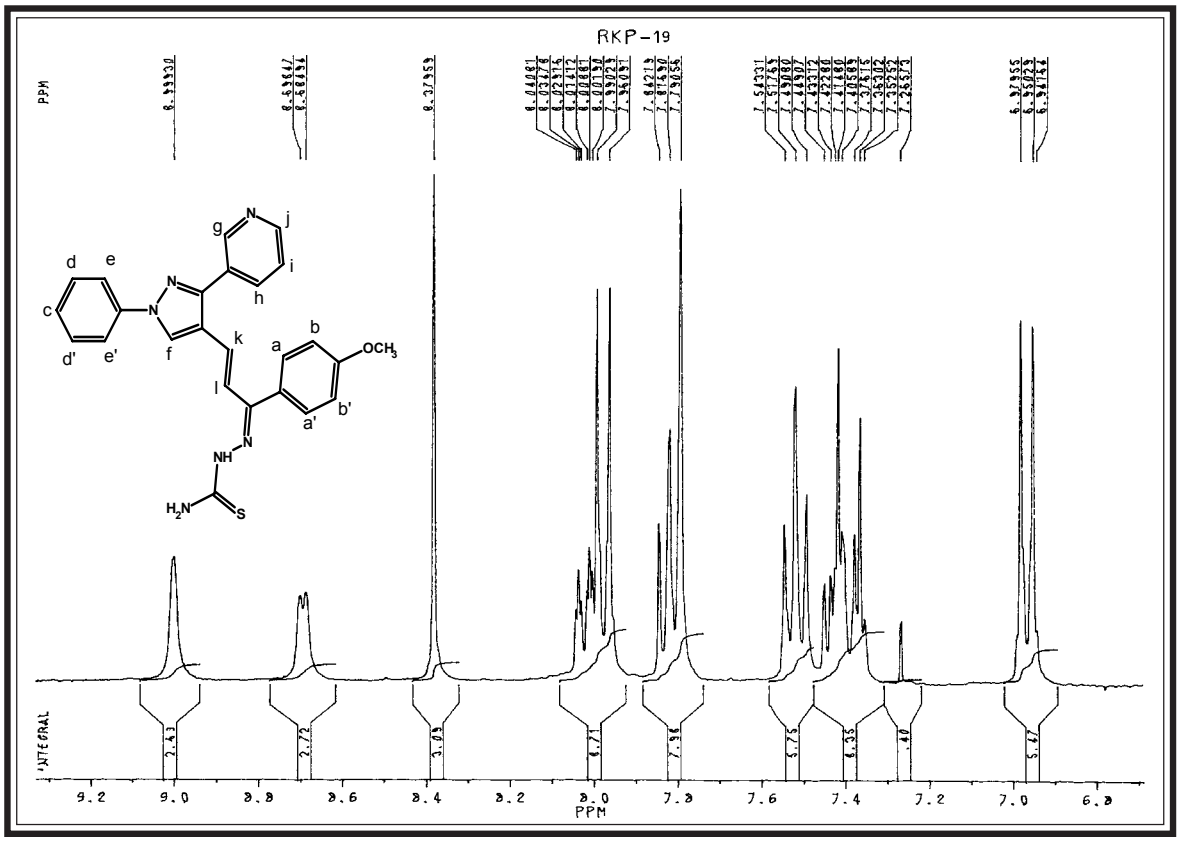
PMR SPECTRAL STUDY OF 1-(p-ANISYL)-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONE

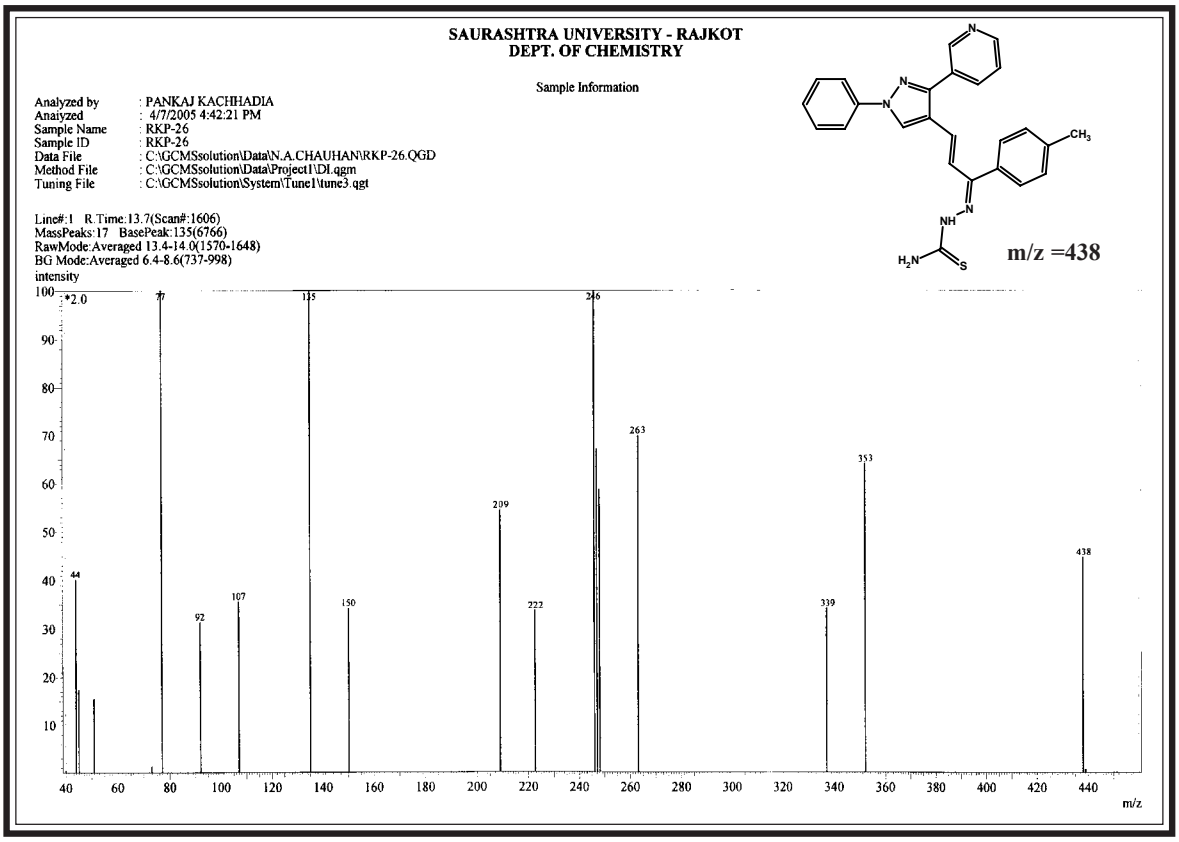


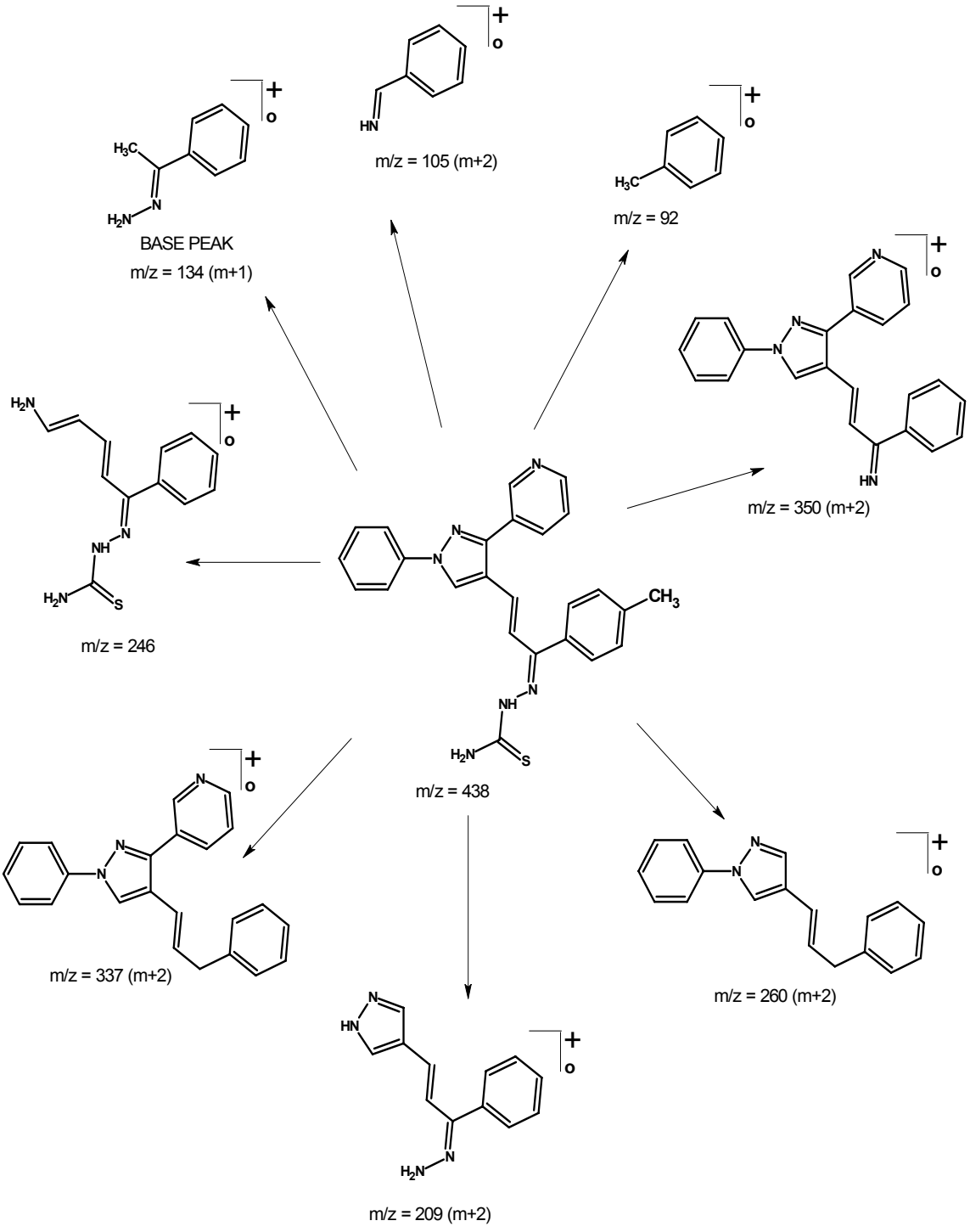
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	7.34-7.39	1H	doublet	Vin.Hm	Jml=15.5
2	7.51-7.57	3H	multiplet	Ar-Hh,aa'	-
3	7.63-7.67	3H	multiplet	Ar-Hc,dd'	-
4	7.79-7.81	2H	doublet	Ar-Hbb'	Jbb'=7.5
5	7.81-7.85	1H	doublet	Vin.Hl	Jlm=14.9
6	7.81-7.84	2H	doublet	Ar-Hee'	Jee'=8.3
7	8.23-8.25	1H	doublet	Ar-Hf	-
8	8.41	1H	singlet	Ar-Hk	-
9	8.71-8.73	1H	multiplet	Ar-Hg	-
10	9.08	1H	singlet	Ar-Hj	Jjk=7.60

EXPANDED AROMATIC REGION






m/z = 105 (m+2)
m/z = 92
BASE PEAK
m/z = 134 (m+1)
m/z = 350 (m+2)
m/z = 246
m/z = 438
m/z = 337 (m+2)
m/z = 260 (m+2)
m/z = 209 (m+2)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONES

[A] Synthesis of 1,N-Phenyl-3-â-pyridyl-4-formyl pyrazole

See Part-I, Section-I (B).

[B] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-II (B).

[C] Synthesis of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-thiosemicarbazone

A mixture of 1-(p-Tolyl)-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propen-1-one (3.65 g, 0.01 M) in ethanol & thiosemicarbazide (0.91 g, 0.01 M) in ethanol (20 ml.)containing catalytic amount of acetic acid was refluxed for 8 hrs. on water bath. The reaction mixture was then cooled and diluted with cold water, crude product was isolated, crystallised from ethanol. Yield 58%, m.p. 120^{o}C ($C_{25}H_{22}N_6S$; Found : C, 68.40%; H, 5.06%; N, 19.14%; Requires : C, 68.47%; H, 5.01%; N, 19.16%).

Similarly other cyanopyrans have been obtained. The physical data are recorded in Table No. 9.

[D] Antimicrobial activity of 1-Aryl-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-thiosemicarbazones

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solutions are recorded in Graphical Chart No.9.

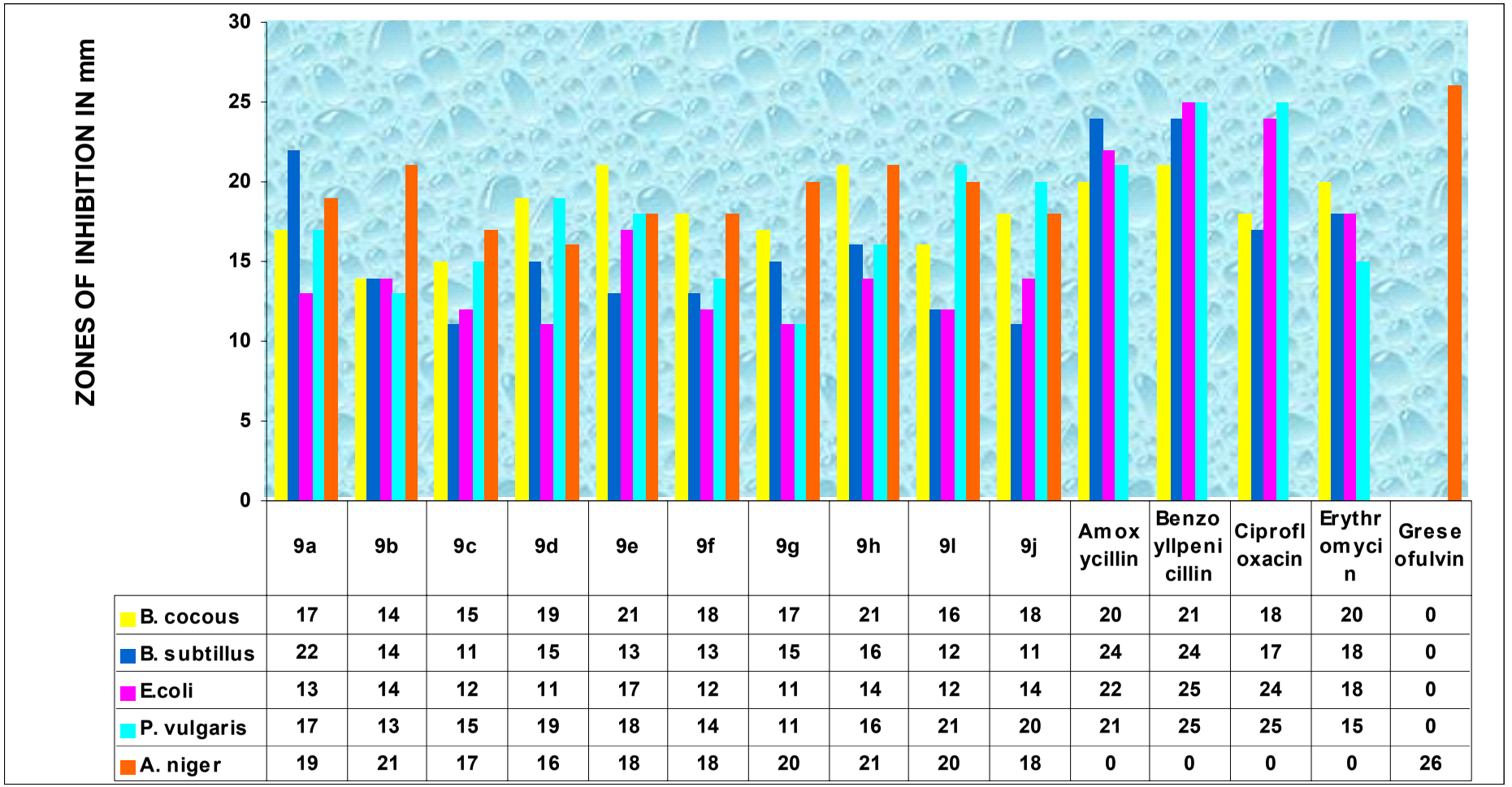
TABLE NO. 9 : PHYSICAL CONSTANTS OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2 -PROPENE-1-THIOSEMICARBAZONE

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
9a	4-CH_3-C_6H_4-	$C_{25}H_{22}N_6S$	438	120	0.50	58	19.16	19.14
9b	4-OCH_3-C_6H_4-	$C_{25}H_{22}N_6OS$	454	134	0.54	54	18.49	18.46
9c	2-OH-C_6H_4-	$C_{24}H_{20}N_6OS$	440	180	0.33	52	19.08	19.05
9d	4-OH-C_6H_4-	$C_{24}H_{20}N_6OS$	440	186	0.42	60	19.08	19.06
9e	4-Cl-C_6H_4-	$C_{24}H_{19}ClN_6S$	458.5	170	0.50	58	18.31	18.28
9f	4-F-C_6H_4-	$C_{24}H_{19}FN_6S$	442	154	0.37	64	18.99	18.95
9g	4-Br-C_6H_4-	$C_{24}H_{19}BrN_6S$	503	206	0.41	68	16.69	16.67
9h	3-NO_2-C_6H_4-	$C_{24}H_{19}N_7O_2S$	469	179	0.52	49	20.88	20.85
9i	4-NO_2-C_6H_4-	$C_{24}H_{19}N_7O_2S$	469	188	0.60	45	20.88	20.86
9j	4-NH_2-C_6H_4-	$C_{24}H_{21}N_7S$	439	146	0.57	65	22.31	22.28

*TLC Solvent System : Acetone : Benzene

2 : 8

GRAPHICAL CHART NO.9 : ANTIMICROBIAL ACTIVITY OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONES



	9a	9b	9c	9d	9e	9f	9g	9h	9l	9j	Amoxycillin	Benzoyllpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	17	14	15	19	21	18	17	21	16	18	20	21	18	20	0
B. subtillus	22	14	11	15	13	13	15	16	12	11	24	24	17	18	0
E.coli	13	14	12	11	17	12	11	14	12	14	22	25	24	18	0
P. vulgaris	17	13	15	19	18	14	11	16	21	20	21	25	25	15	0
A. niger	19	21	17	16	18	18	20	21	20	18	0	0	0	0	26

BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONES

	Antibacterial Activity zone of inhibition in mm			Antifungal Activity zone of inhibition in mm
B. cocous	*B. subtillus*	*E. coli*	*P. vulgaris*	*A. niger*
1	2	3	4	5
9e(21)	9a(22)	9e(17)	9i(21)	9b(21)
9h(21)			9h(21)	9h(21)
9d(19)			9d(19)	9g(20)
9f(18)			9e(18)	9g(20)
9j(18)				
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

SECTION- II

MICROWAVE INDUCED AN EXPENDITOUS SYNTHESIS OF 1-ARYL-3-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOLE-4'-YL)-2-PROPENE-1-THIOSEMICARBAZONE

The use of domestic microwave oven in this regard is now a well established procedure in MORE[370](Microwave Induced Organic Reaction Enhancement). It has been reported that the rate of variety of organic reaction such Diels-Alder[371,372], Claisan reaction [373,374], oxidation[375-376], reduction[377], diacetylation[378,379], deacetylation[380], esterification[381], hydrolysis of esters[382,383], Doebner condensation[384], Knoevenagel condensation[385] could be enhanced by microwave irradiation.

Recent days, domestic microwave oven is useful to prepare isoflavons[386], formazans[387], chalcones[388], quinazolinones[389], benzofurans[390]and pyrazolines[391-394]. The name reaction such as Biginelli[395], Prins[396], Cannizzaro[397]and cross Cannizzaro[398], Michael addition[399], Fries migration[400], Wolff-Kishner reduction[401], Gould Jacobs reaction[402], Beckmann reaction[403], Tendem-Fries[404], Aldol[405]can also be performed by domestic microwave oven.

As a part of on going research towards the non traditional approach to the experimental setup of organic reaction, the concept of microwave enhanced reaction has been utilized for rapid and efficient synthesis of 1-Aryl-3-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl)-2-propene-1-thiosemicarbazone. Q. Pro-M Microwave oven, Questron technologies corporation-CANADA, sample preparation system : 220 VAC, 60 Hz is used as a microwave irradiation source and data are compared in terms of yield and reaction period and have been cited in Table No. 9a.

TABLE NO. 9a : COMPARISION OF CONVENTIONAL AND MICROWAVE ENHANCED SYNTHESIS OF THIOSEMICARBAZONES

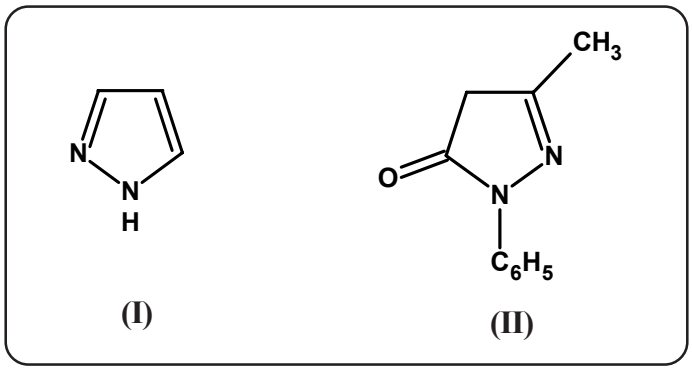
Comp. No.	R	Thermal		Microwave		M.P. °C
		Reaction Period (hr.)	Yield %	Reaction Period (min.)	Yield %	
9a	4-CH_3-C_6H_4-	8	58	9	62	120
9b	4-OCH_3-C_6H_4-	8	54	10	57	134
9c	2-OH-C_6H_4-	8	52	9	56	180
9d	4-OH-C_6H_4-	8	60	9	63	186
8e	4-Cl-C_6H_4-	8	58	11	61	170
9f	4-F-C_6H_4-	8	64	9	67	154
9g	4-Br-C_6H_4-	8	68	10	70	206
9h	3-NO_2-C_6H_4-	8	49	7	52	179
9i	4-NO_2-C_6H_4-	8	45	11	48	188
9j	4-NH_2-C_6H_4-	8	65	9	69	146

INTRODUCTION

Pyrazoles are well known five membered heterocyclic compounds and several procedure for there synthesis have been extensively studied. Such studies have been stimulated by various promising applications, especially in the case of N-substituted pyrazole derivatives. In fact, certain N-substituted pyrazoles are used as pharmaceuticals e.g. analgesic, anti-inflammatory, antipyretic, agrochemicals whereas some other is being studied for their medicinal interest.

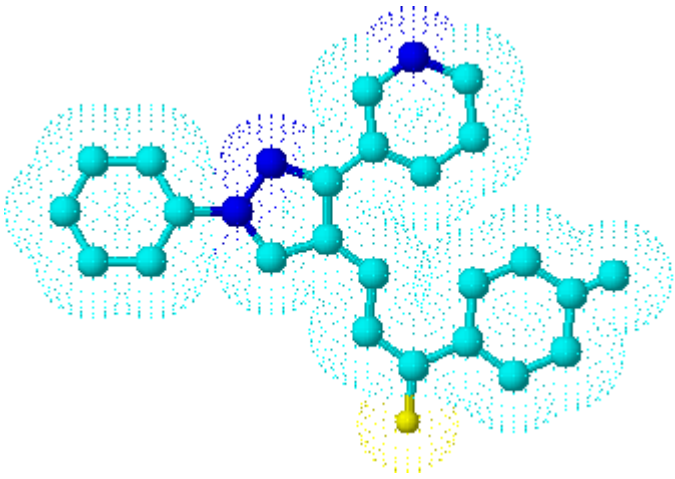
The knowledge of such applications has pointed out that N-substituted pyrazoles are important target to be prepared to our interest on the synthesis and molecular structure determination of some types of pyrazoles.

The pyrazole ring system (I) consists of a doubly unsaturated five membered ring containing two adjacent nitrogen atoms. Knorr[406,407] first synthesized a compound containing this system in 1883 by a reaction of ethylaceto acetate with phenylhydrazine, which yield 1-phenyl-3-methyl-5-pyrazolone (II).



(I) (II)

Knorr[408] introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by replacement of carbon by nitrogen. Since many drugs and dyes contain the pyrazole nucleus, the class has been widely studied.



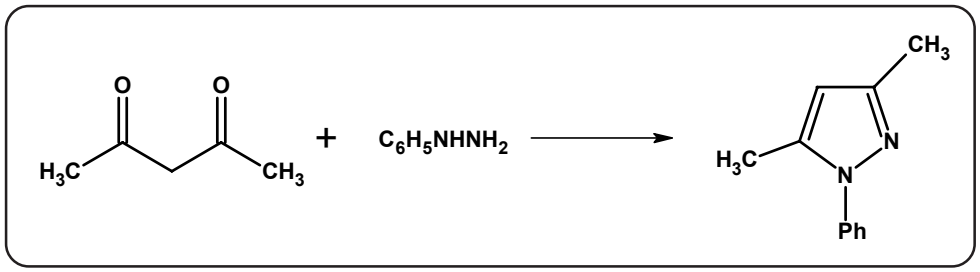
[B]

STUDIES ON PYRAZOLES

SYNTHETIC ASPECT

Various methods for the preparation of pyrazoles have been cited in literature.

1. The reaction of hydrazine or its derivatives such as alkyl or aryl hydrazines, semicarbazine or aminoguanidine with 1,3-dicarbonyl compounds.



2. The reaction of hydrazines with α,β-unsaturated carbonyl compounds.
3. The reaction of aliphatic diazo compounds such as diazomethane or diazoester with acetylene or olefins.

THERAPEUTIC IMPORTANCE

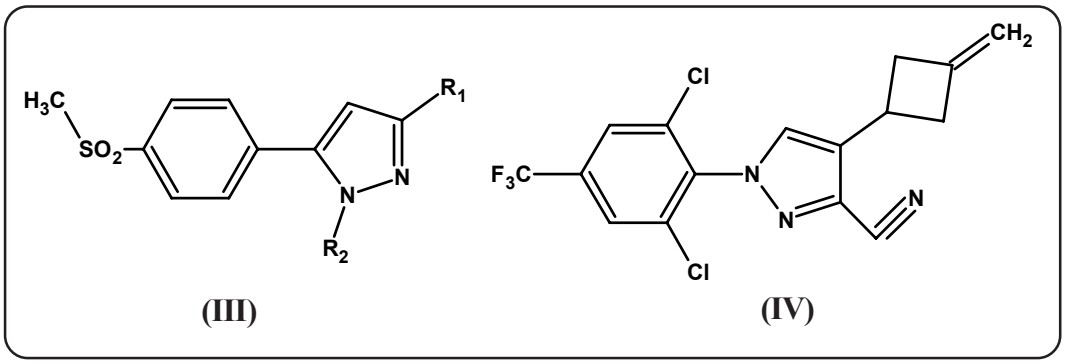
Much research has been carried out with the aim to finding therapeutic values of pyrazole moiety since their discovery. A large number of substituted pyrazole derivatives are prepared and tested for variety of biological activities like.

1. Antiinflammatory[409,410]
2. Insecticidal[411]
3. p-38 Kinase inhibitors[412-415]
4. Antiepileptic[416]
5. Nematicidal[417]
6. Antitumor[418]
7. Anticancer[419]
8. Antiviral[420]
9. Herbicidal[421-424]
10. AntiHIV[425]

Jansen Karte et. al.[426] have synthesized pyrazole derivatives as pesticides.

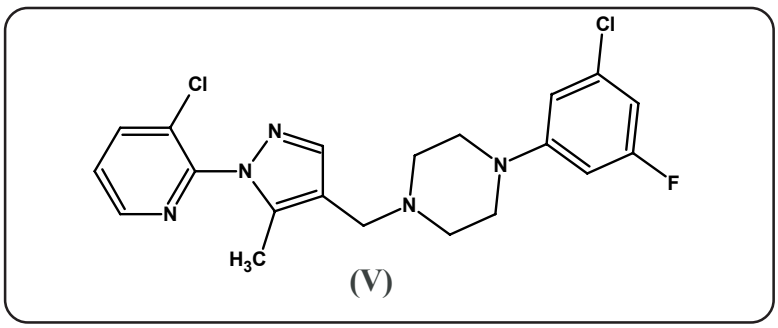
Somega Shinzo and co-workers[427] have synthesized pyrazole derivatives and reported their herbicidal activity. Geheing Reinhald et. al.[428] have synthesized 5-amino-4-cyano-1-aryl-pyrazoles and shown them as plant growth inhibitors. Nakamura Katsyga and co-worker[429,430] have prepared 1,5-diphenyl pyrazoles as Cox-2-inhibitors (III).

Pier Giovanni Baraldi et. al.[431] have synthesized pyrazole derivatives as antileukemic agents. Thomas Alan Crowell et. al.[432] prepared new pyrazoles as selective α-adrenergic agonists. Kevin M. Moore et. al[433] prepared pyrazoles as human dopamine-D4-receptors while Bernard Banks et. al.[434] have synthesized pyrazole derivatives (IV) and tested for their antiparasitic activity.



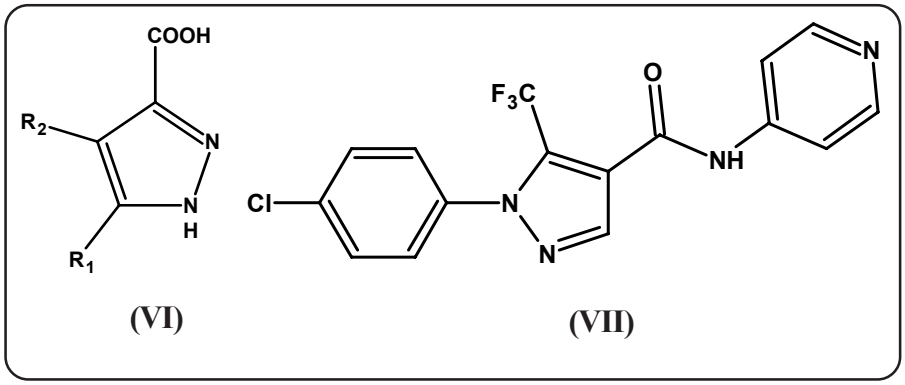
Laborde Edgardo et. al.[435] have found that pyrazoles possess glycine transporter-2-inhibitor activity. Andrew Thurkaub et. al.[436] have synthesized high affinity C5a receptor modulator pyrazoles. Nagaaki Sato et. al.[437] have prepared pyrazoles as neuropeptide T5 receptor antagonist. G. M. Hi Yamanonch[438] has prepared pyrazoles as glycine transporter protein inhibitors.

Feid-Allah Hassan[439] have prepared pyrazoles and reported their antidiabetic and antibacterial activity. Ejima Akio et. al[440] have synthesized pyrazole derivatives as antitumor agents (V).



Jacques Dumas and co-workers[441] have synthesized pyrazole derivatives as rafkinase and angiogenesis inhibitor agents. David L. S. et. al.[442] have reported pyrazoles as activators of the nitrile oxide receptor and soluble guanglate cyclase agent. T Van Herk et. al.[443] have demonstrate pyrazoles as nicotinic acid receptor (VI). Barber Christopher et. al.[444] have synthesized pyrazole derivatives as phosphodiesterase inhibitors.

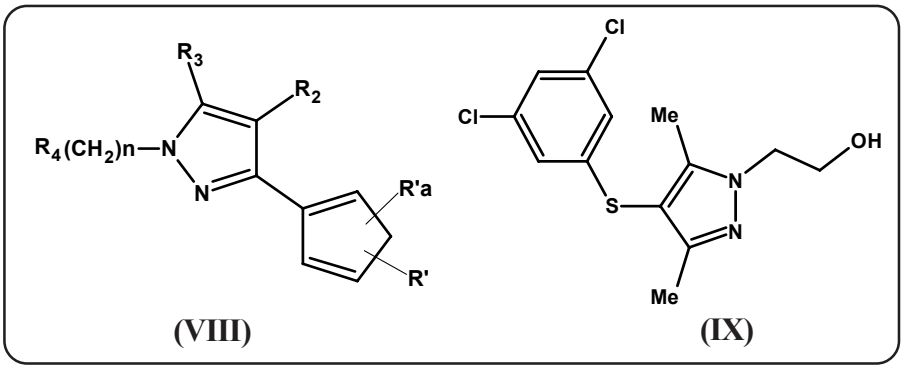
Recently, Atkinson R. N. et. al.[445] have synthesized pyrazoles as sodium channel Blocker (VII). Murakanii Hiroshi et. al.[446] have synthesized pyrazoles as antifouling agent. Gellibert Francoise et. al.[447] have prepared pyrazole derivatives as TGF-13 inhibitors.



(VI) (VII)

Grazid Mamalo et. al.[448] have newly synthesized pyrazole derivatives tested for antimicrobial activity. R. Y. Huang and co-workers[449] have prepared some 1,2,4- triaryl-4-alkyl-pyrazoles as estrogen receptor. C. Vittoria and co-workers[450] have prepared some pyrazoles as adenosine receptor antagonists.

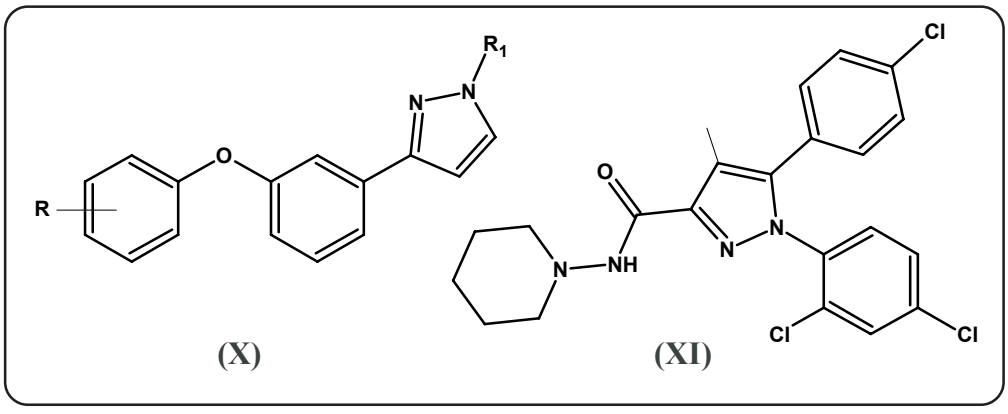
Schindler Ursula et. al.[451] synthesized new pyrazole derivatives (VIII) as cardiovascular agents. Havaldar Freddy et. al.[452] synthesized 4,5-dihydro 3-phenyl-1H-pyrazole and reported their biological activity. Carbau Romuald and co-workers[453] have prepared pyrazole derivatives (IX) useful as reverse transcriptase inhibitors for the treatment of HIV infection.



(VIII) (IX)

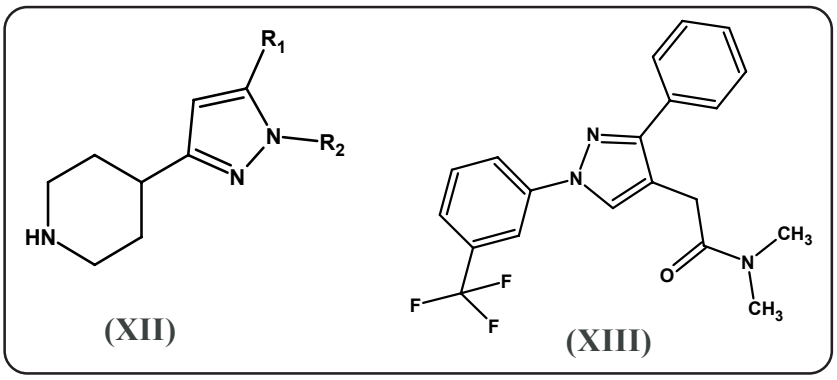
Nishimura Tsoshihiro et. al.[454] have synthesized pyrazoles as inhibitors of human SGLT2 (sodium dependent glucose transporter-2). From Recent literature it has found that pyrazole derivatives possesses a number of biological activities, such as fungicidal,[455-456]herbicidal,[457-460] cardiovascular,[461]antiinflammatory,[462-464] Cox-II inhibitor,[465] antimicrobial,[466]anticancer,[467-469] protein kinase inhibitor,[470-473] antibacterial[474,475]antiviral,[476]antiparasitic,[477]HIV reverse transcriptase inhibitor[478,479]and 5-H T2O receptors.[480-482]

Ji Yang et. al[483] have documented 3-(4-phenoxyphenyl)pyrazole derivatives (X) for their Sodium Channel Blockers. Ruoxi Lan et. al.[484] have prepared pyrazole derivatives as Cannabinoid receptor antagonist (XI).

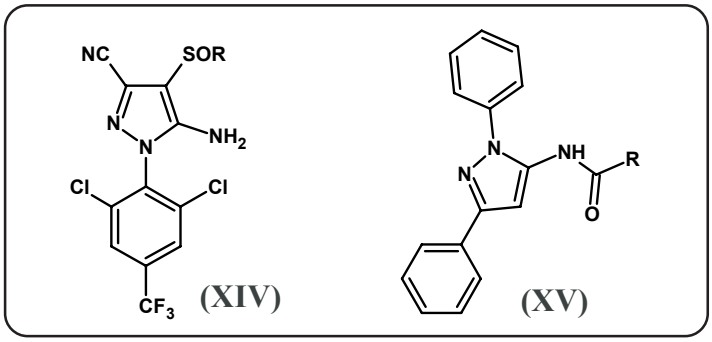


(X) (XI)

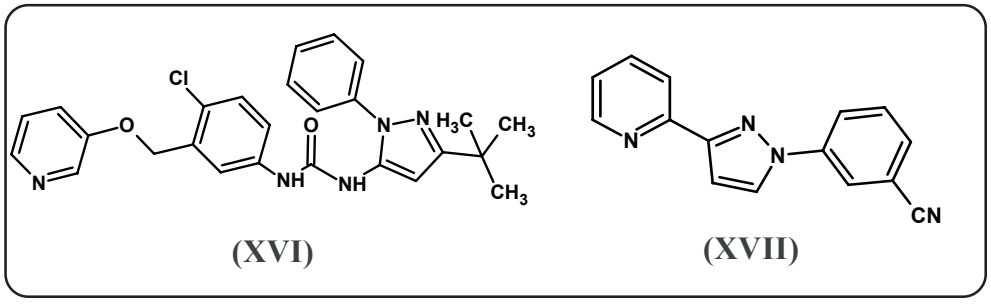
Akihiko Tanitame et. al.[485] have synthesized pyrazole derivatives (XII) as antibacterial activity and selective inhibitory activity against bacterial topoisomerases. Gregory R. Bebernitz et. al.[486]have described 1,3-diaryl-[1H]-pyrazole-4-acetamide as antidiabetic agents (XIII). Franco chimenti, Adriana Bolasco et. al[487]have synthesized pyrazole derivatives as Monoamine Oxydase Inhibitors.



Abdel-rahman farghaly and hussein el-kashef et. al.[488] have prepared pyrazole derivatives as antibacterial and antifungal activities. Pierluigi caboni et. al.[489] have reported phenylpyrazole as insecticide action(XIV). Craig W. Lindsley et. al.[490]have discovered positive allosteric Modulators for the Metabotropic Glutamate Receptor from a series of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamides that potentiate receptor function *in vivo*(XV).



Adrian l. Gill and Martyn Frederickson et. al.[491]have identified pyrazole as a novel p38 MAP kinase inhibitors(XVI). Jeffrey roppe et. al.[492] have discovered novel heteroaryl azoles that are metabotropic glutamate receptor antagonists with anxiolytic activity(XVII).



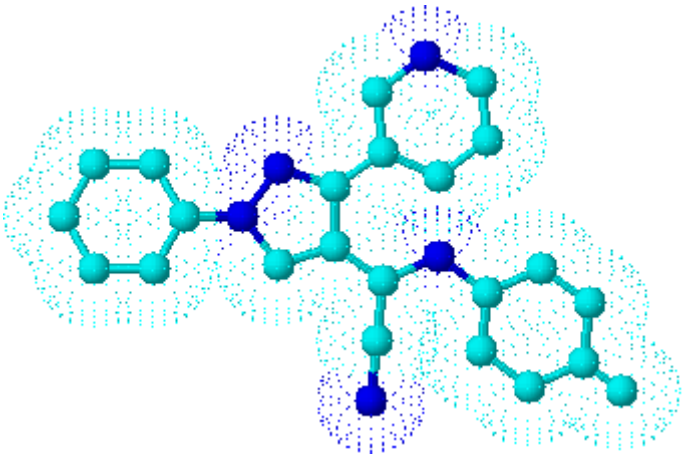
Literature survey reveals that the compounds bearing pyrazole moiety possess potential drug activity. Looking to the diversified biological activity, it appeared of interest to synthesize some á-arylaminonitriles, azomethines and thiazolidinones bearing pyrazole moiety, in order to achieving compounds having better therapeutic importance. These studies are described in following parts.

STUDIES ON PYRAZOLES :

PART - VIII : STUDIES ON á-ARYLAMINONITRILES

PART - IX : STUDIES ON N-ARYL-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINES

PART - X : STUDIES ON THIAZOLIDINONES



PART - VIII

STUDIES ON

α-ARYLAMINONITRILES

INTRODUCTION

The nitriles have been widely studied because of their industrial and biological applications. Several nitrile derivatives have been used in agriculture field becuse of their high toxicity. The first synthesis of nitriles was reported by Wohler and Liebig[493] in 1832 and by pelouze[494] in 1834. The nitriles are very useful intermediate for various product such as acrylonitrile for plastics, synthetic rubber, fibers and phthalonitriles for a dye stuff.

SYNTHETIC ASPECT

Various methods for the preparation of nitriles have been reviewed by David Mowry.[495] Few recent procedures are as mentioned below.

(I) From halides using NaCN, Al_2O_3[496].

(II) From alkyl halides using KCN, tetraalkylammonium salt and water in trace[497]

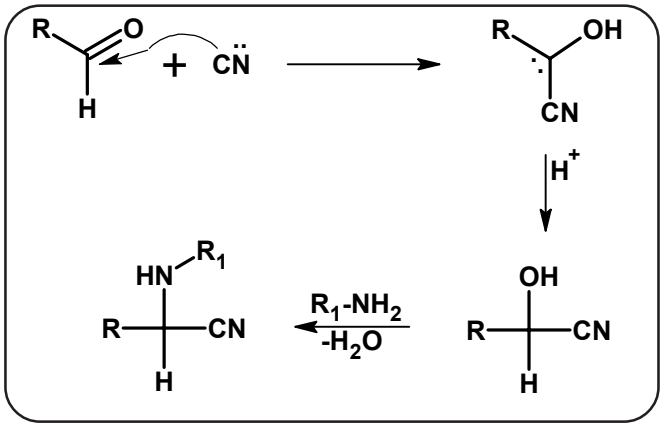
(III) Preparation by metathesis[498]

(IV) Dehydrating amides using $POCl_3$[499]

(V) The pyrolysis of Schiff's bases[500]

(VI) A practical method for the preparation of nitriles from primary amines under microwave irradiation, has been reported.[501-503]

MECHANISM :



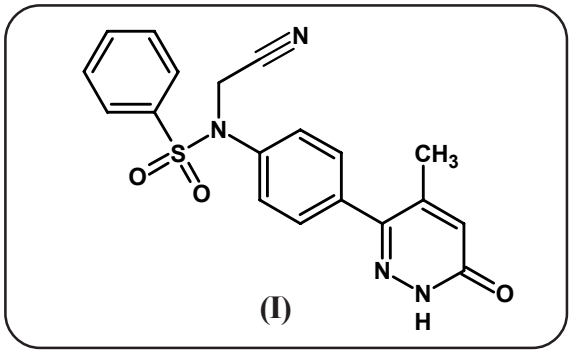
From the above reaction, it can be seen that a nucleophile (CN) attacks on the carbonyl carbon of aldehyde and yields cyanohydrine which reacts with amine to yield nitrile derivatives.

THERAPEUTIC IMPORTANCE

Various biological activities are associated with nitriles, which can be enlisted as under.

1. Antiarrythemic[504]
2. Pesticidal[505]
3. Herbicidal[506]
4. Fungicidal[507]
5. CNS stimulants[508]
6. Antimicrobial[509,510]
7. Antihypertensive[511]
8. Antihypoxic[512]
9. Antiinflammatory[513]

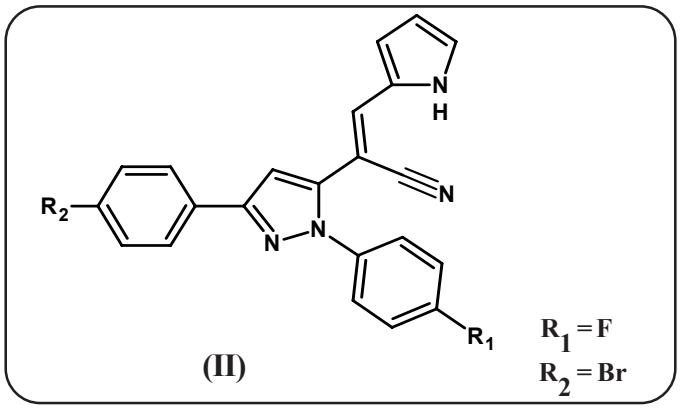
Nitriles with fused pyridine rings were reported as ulcer inhibitor.[514] Nobuyuki et. al.[515] have prepared some new nitriles (I) and reported them as tumor necrosis factor production inhibitors.



(I)

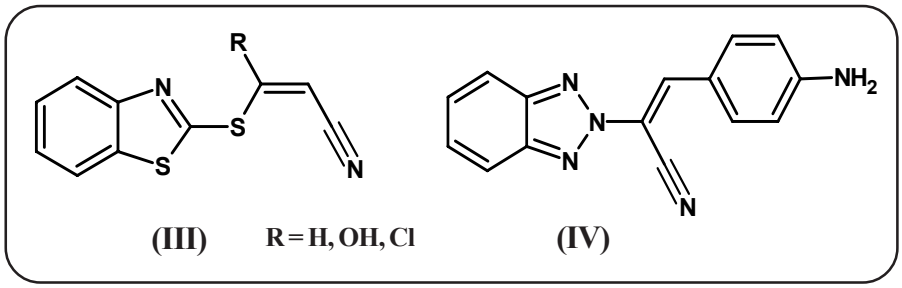
Kobayashi et. al.[516] have synthesised nitrile derivatives. The nitriles as a refrigeration lubricating oil have been reported by Sabani and co-workers.[517] Peterson I. A. and co-workers[518] have studied the antineoplastic activity of some aminonitriles.

V. S. Parmar and co-workers[519] have prepared a series of nitriles (II) and reported them as antioxidants. Antimicrobial activity of nitriles bearing quinoline moiety has been reported by A. R. Parikh and co-workers.[520]



(II)

Nosyruva and co-workers[521] have prepared some new nitrile derivatives (III) and screened for their biological activities.



(III) R = H, OH, Cl (IV)

P. Sanna and co-workers[522] have prepared some novel acrylonitriles (IV) and studied their antituberculor activity. Catherine M. and co-workers[523] have prepared some new cyanoguanidine derivatives and reported them as thromboxane receptor antagonists.

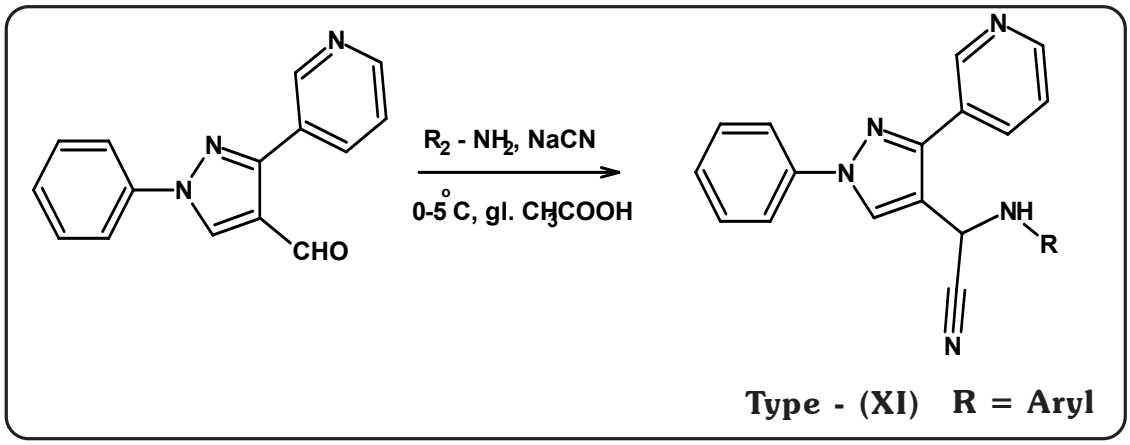
In persuing the work on the nitrile derivatives incorporating pyrazole molecule, the newer nitrile derivatives have been synthesised which have been described as under.

SECTION - I SYNTHESIS AND BIOLOGICAL EVALUATION OF á-ARYLAMINO-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-ACETONITRILES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF á-ARYLAMINO-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-ACETONITRILES

In view of the therapeutic activities of nitriles it was contemplated to synthesise some new nitriles in search of agents possessing higher biological activity. Nitrles of type (XI) have been synthesised by the reaction of 1,N-Phenyl-3-β-pyridyl-4-formyl-pyrazole with different aromatic amines by the presence of sodium cyanide and glacial acetic acid at 0-5^{o}C.



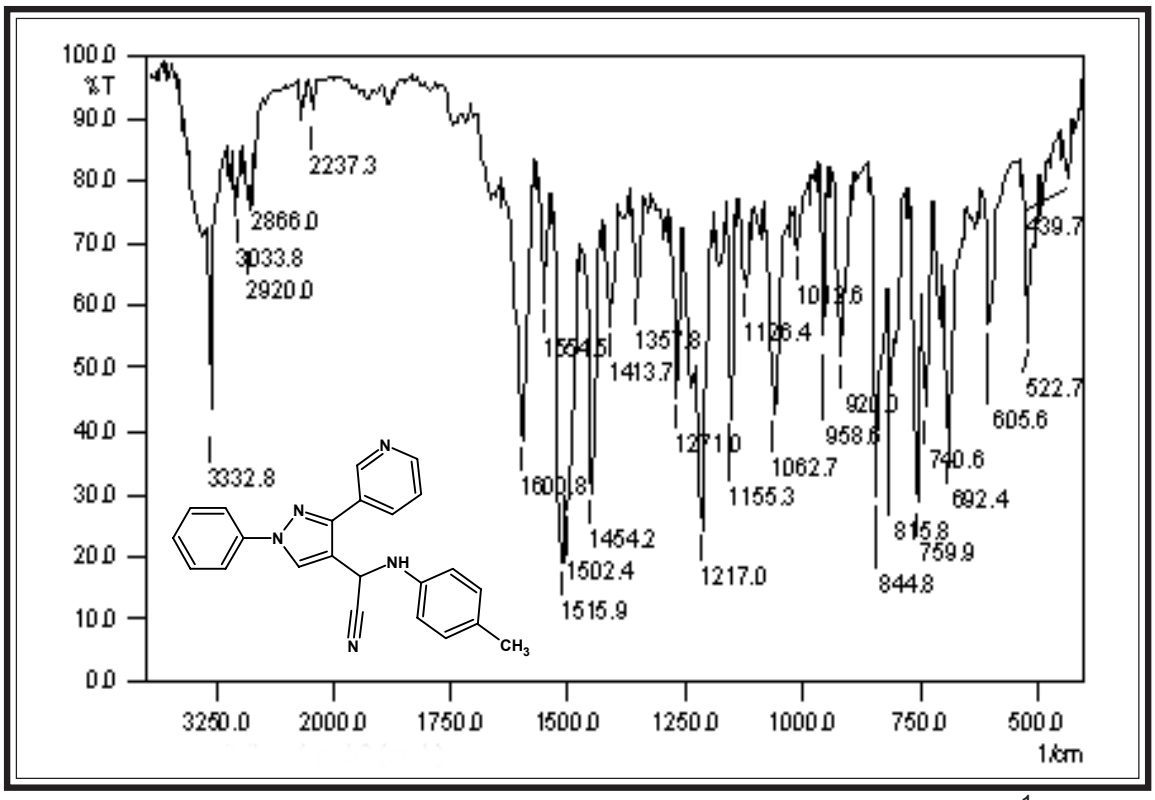
Type - (XI) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. The mass spectra of α-(p-Tolylamino)-1,N-phenyl-3-â-pyridyl-pyrazol-4-yl-acetonitriles give m/z = 337 (recorded on Page No. 159). The fragmentation is also explained (Page No. 160).

The products have been screened for their *in vitro* biological assay like antimicrobial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their *in vitro* biological assay like antitubercular activity towards a strain of *Mycobacterium tuberculosis* $H_{37}Rv$ at concentration of 6.25 mg/ml using Rifampin as standard drug.

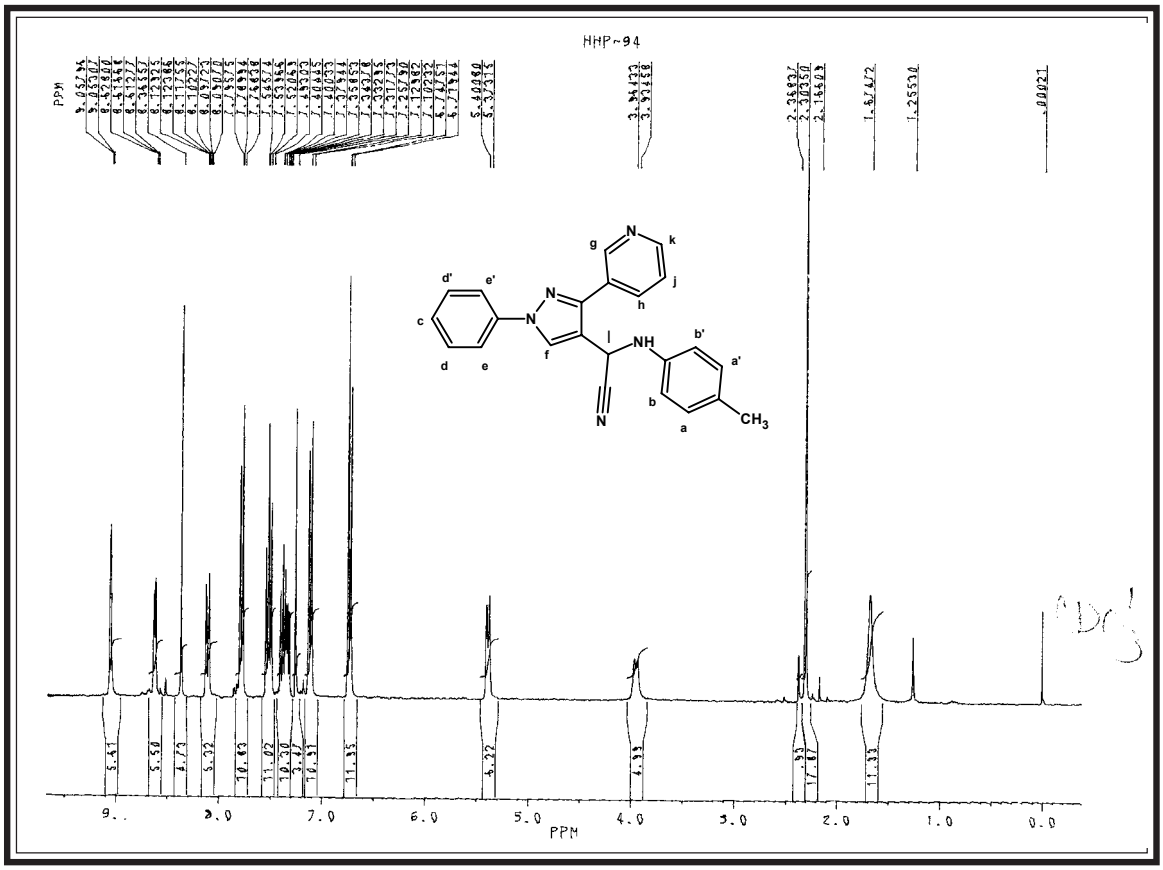
IR SPECTRAL STUDY OF á-(p-TOLYLAMINO)-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-ACETONITRILE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2920	2975–2920	95
$-CH_3$	C – H str. (sym.)	2866	2880–2860	"
	C – H i.p. (def.)	1454	1470–1435	"
	C – H o.o.p. (def.)	1357	1395–1370	"
Aromatic	C – H str.	3033	3090–3030	96
	C = C str.	1554	1520–1480	"
	C – H i.p. (def.)	1126	1125–1090	"
		1062	1070–1000	"
	C – H.o.o.p (def.)	815	835–810	"
Pyrazole	C = N str.	1600	1610–1590	96
moety	C – N str.	1217	1230–1220	"
	C = C str.	1515	1585–1480	"
Nitrile	C ≡ N str.	2237	2240–2220	95
	N – H str. (sym.)	3332	3450–3200	"

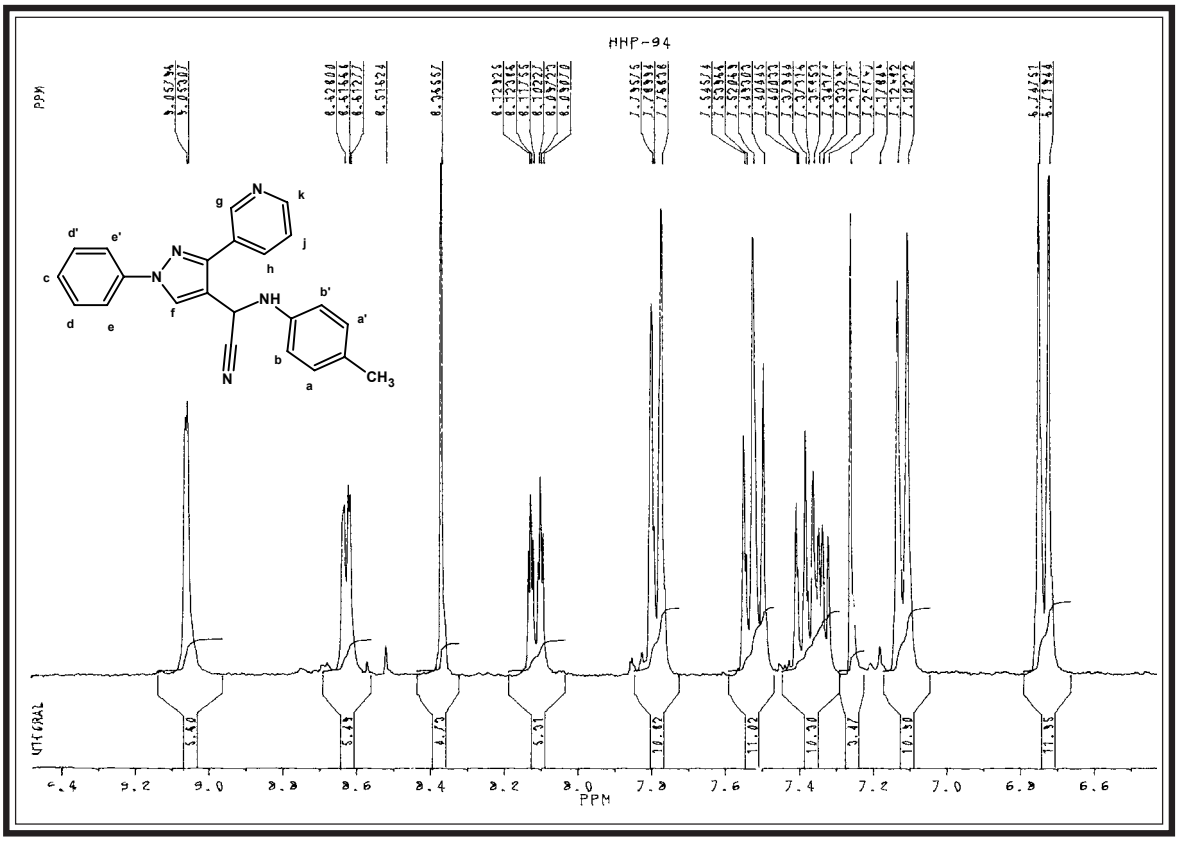
PMR SPECTRAL STUDY OF á-(p-TOLYLAMINO)-1,N-PHENYL-3-â-pyridyl-PYRAZOL-4-YL ACETONITRILE

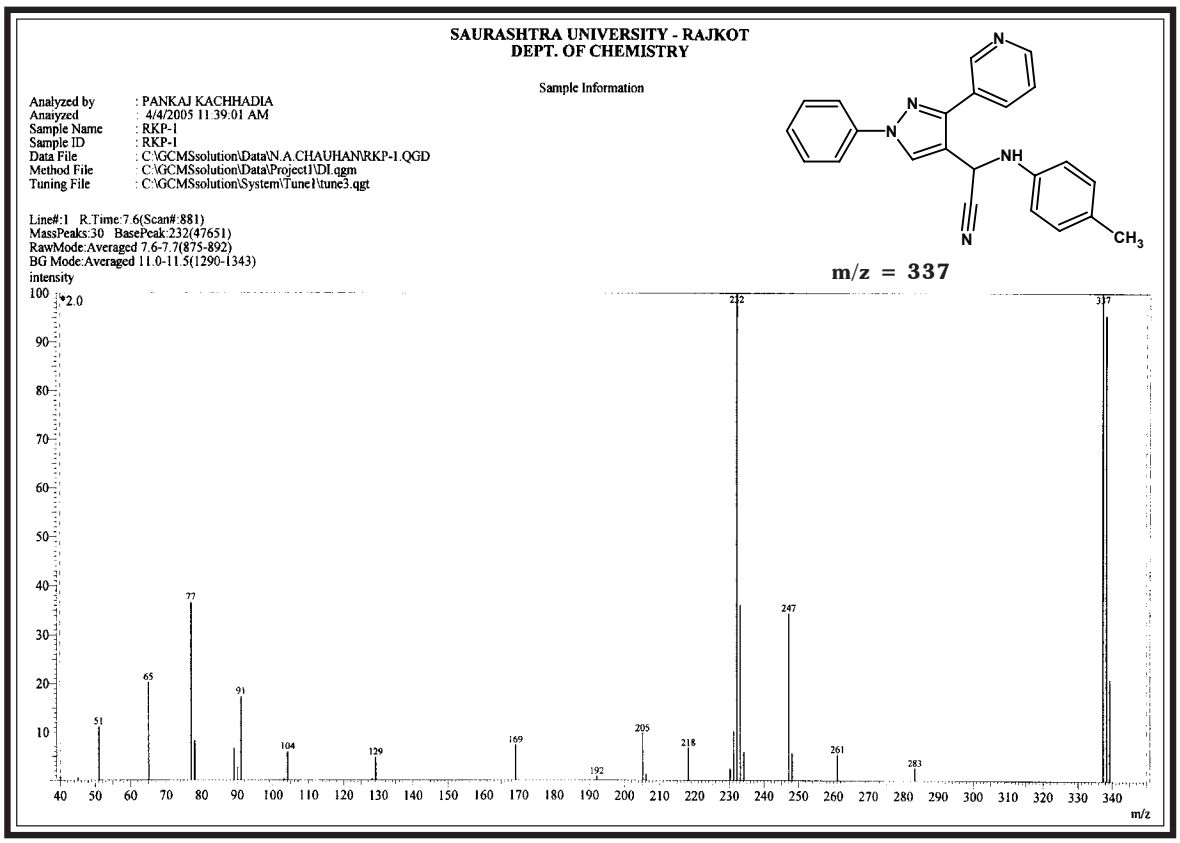


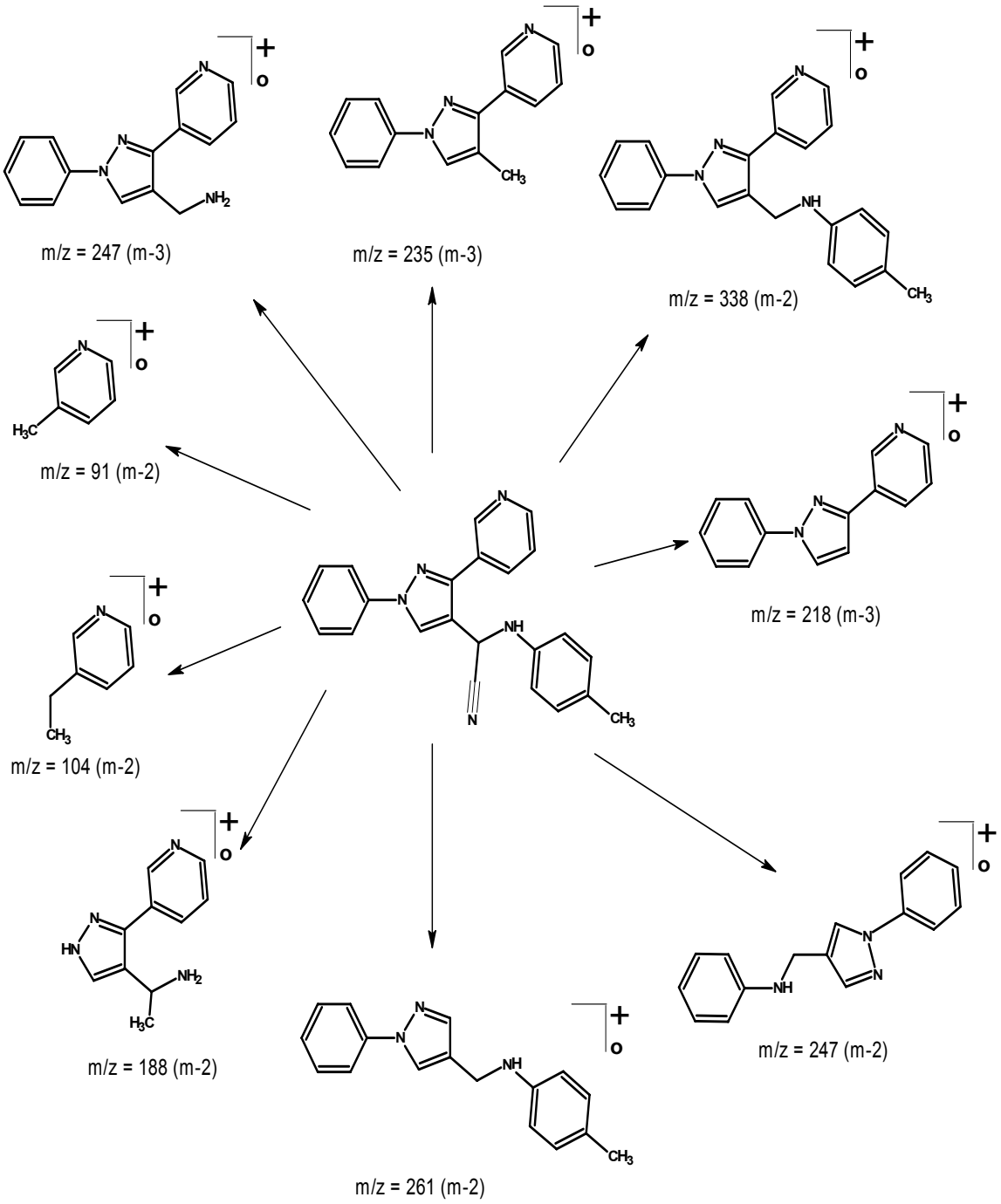
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.36	3H	singlet	Ar-CH_3	-
2	3.96	1H	singlet	-NH	-
3	5.40	1H	singlet	Ar-Hl	Jbb'=7.9
4	6.71-6.74	2H	doublet	Ar-Ha,a'	Jaa'=8.4
5	7.10-7.13	2H	doublet	Ar-Hb,b'	Jbb'=6.8
6	7.31-7.40	1H	multiplet	Ar-Hh	-
7	7.49-7.54	3H	multiplet	Ar-Hc,d,d'	-
8	7.76-7.79	2H	doublet	Ar-He,e'	Jee'=8.2
9	8.09-8.12	1H	multiplet	Ar-Hj	-
10	8.36	1H	singlet	Ar-Hf	-
11	8.61-8.63	1H	doublet	Ar-Hk	Jkj=6
12	9.05	1H	doublet	Ar-Hg	Jgk=1.5

EXPANDED AROMATIC REGION






m/z = 247 (m-3)
m/z = 235 (m-3)
m/z = 338 (m-2)
m/z = 91 (m-2)
m/z = 218 (m-3)
m/z = 104 (m-2)
m/z = 188 (m-2)
m/z = 247 (m-2)
m/z = 261 (m-2)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF á-ARYLAMINO-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-ACETONITRILES

[A] Synthesis of 3-Acetylpyridine phenyl hydrazone

See, Part-I, Section-I (A).

[B] Synthesis of 1N-Phenyl-3-â-pyridyl-4-fromyl-pyrazole

See, Part-I, Section-I (B).

[C] Synthesis of á-(p-Anisylamino)-1,N-phenyl-3-â-pyridyl-pyrazol-4-yl-acetonitrile

1N-Phenyl-3-β-pyridyl-4-formyl pyrazole (2.65g, 0.01M) dissolved in ethanol (20 ml) was added to sodium cyanide (0.48g, 0.01M) dissolved in water (5 ml) followed by glacial acetic acetic acid (5 ml). The contents were then stirred for 5 minutes to form cyanohydrin at 0^{o}C. p-Anisidine (1.23g, 0.01M) dissolved in methanol was added to the reaction mixture, contents were kept at room temp. for 24 hrs. and poured into ice. The solid product was crystallized from DMF. Yield, 57%, m.p. 199^{o}C ($C_{23}H_{19}N_5O$; Found : C, 68.43%; H, 4.15%; N, 18.33%; Requires : C, 68.48%; H, 4.18%; N, 18.36%).

Similarly, other nitriles were prepared. The physical constants are recorded in Table No.10.

[D] Antimicrobial activity of á-Arylamino-1,N-phenyl-3-â-pyridyl-pyrazol-4-yl-acetonitriles

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solution are recorded in Graphical Chart No. 10.

Antitubercular screening of the compounds of type(XI) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-II (C) and the percentage of inhibition data of the compounds are recorded in Table No. 10a.

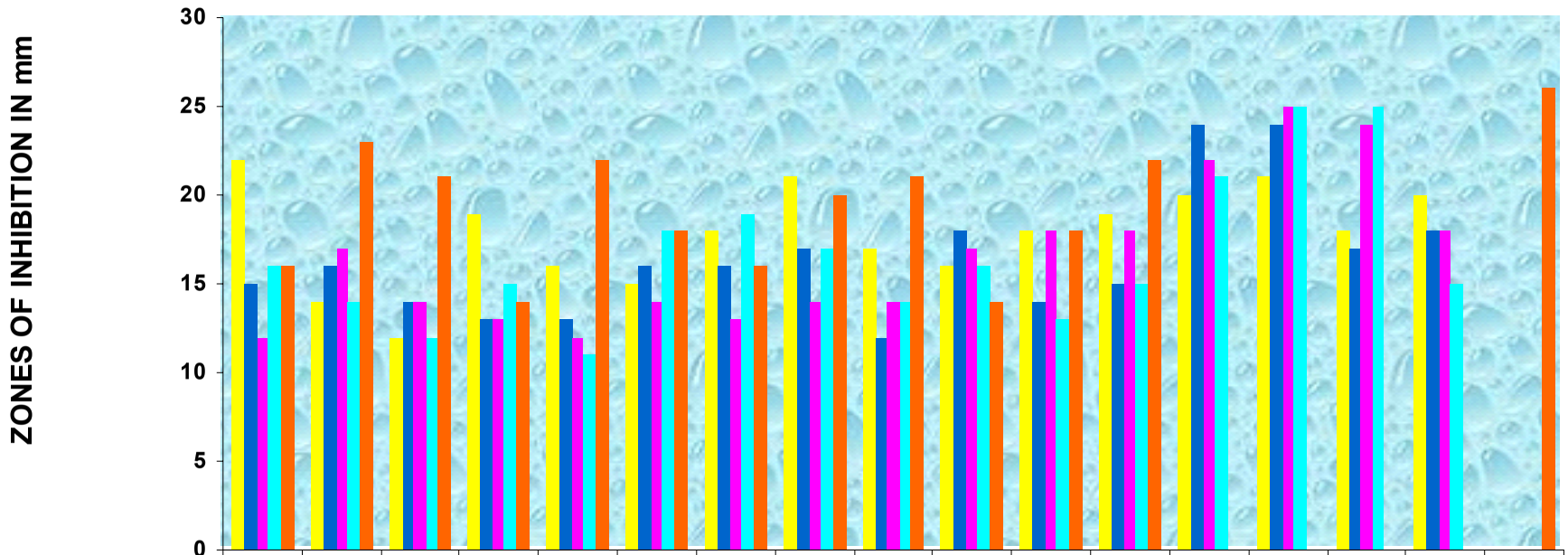
TABLE NO. 10 :PHYSICAL CONSTANTS OF á-ARYLAMINO-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-ACETONITRILES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
10a	4-CH_3-C_6H_4-	$C_{23}H_{19}N_5$	365	187	0.61	63	19.16	19.14
10b	4-OCH_3-C_6H_4-	$C_{23}H_{19}N_5O$	381	199	0.57	57	18.36	18.33
10c	2-Cl-C_6H_4-	$C_{22}H_{16}ClN_5$	385.5	206	0.49	52	18.15	18.13
10d	4-Cl-C_6H_4-	$C_{22}H_{16}ClN_5$	385.5	222	0.52	60	18.15	18.14
10e	4-F-C_6H_4-	$C_{22}H_{16}FN_5$	369	176	0.54	63	18.96	18.94
10f	4-Br-C_6H_4-	$C_{22}H_{16}BrN_5$	430	235	0.59	59	16.28	16.26
10g	3-Cl,4-F-C_6H_4-	$C_{24}H_{16}ClFN_5$	403	218	0.63	70	17.34	17.32
10h	3,4-$(Cl)_2$-C_6H_4-	$C_{24}H_{15}(Cl)_2N_5$	420	256	0.43	58	16.66	16.63
10i	2,6-$(Cl)_2$-C_6H_4-	$C_{24}H_{15}(Cl)_2N_5$	420	229	0.38	49	16.66	16.64
10j	2,4-$(CH_3)_2$-C_6H_3-	$C_{24}H_{21}N_5$	379	172	0.51	54	18.46	18.45
10k	2,5-$(OCH_3)_2$-C_6H_3-	$C_{24}H_{21}N_5O_2$	411	208	0.46	56	17.02	16.99
10l	2-NO_2,4-CH_3-C_6H_3-	$C_{23}H_{18}N_6O_2$	410	232	0.39	47	20.48	20.48

*TLC Solvent System : Acetone : Benzene

2 : 8

GRAPHICL CHART NO. 10 :ANTIMICROBIAL ACTIVITY OF á-ARYLAMINO-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-ACETONITRILES

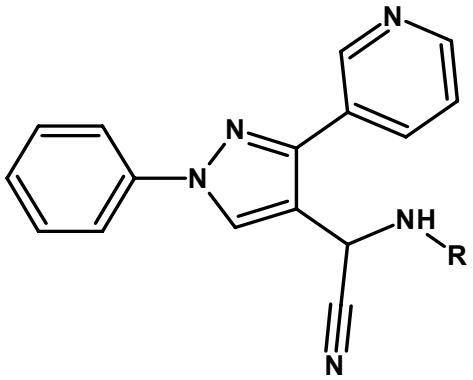


	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Amoxycillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	22	14	12	19	16	15	18	21	17	16	18	19	20	21	18	20	0
B. subtillus	15	16	14	13	13	16	16	17	12	18	14	15	24	24	17	18	0
E.coli	12	17	14	13	12	14	13	14	14	17	18	18	22	25	24	18	0
P. vulgaris	16	14	12	15	11	18	19	17	14	16	13	15	21	25	25	15	0
A. niger	16	23	21	14	22	18	16	20	21	14	18	22	0	0	0	0	26

BIOLOGICAL EVALUATION OF á-ARYLAMINO-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-ACETONITRILES

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	*B. subtillus*	*E. coli*	*P. vulgaris*	*A. niger*
1	2	3	4	5
10a(22)	10j(18)	10k(18)	10g(19)	10b(23)
10h(21)	10h(17)	10l(18)	10f(18)	10e(22)
10d(19)			10h(17)	10l(22)
10l(19)			10a(16)	10c(21)
10g(18)			10d(15)	10i(21)
10k(18)			10l(15)	10h(20)
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

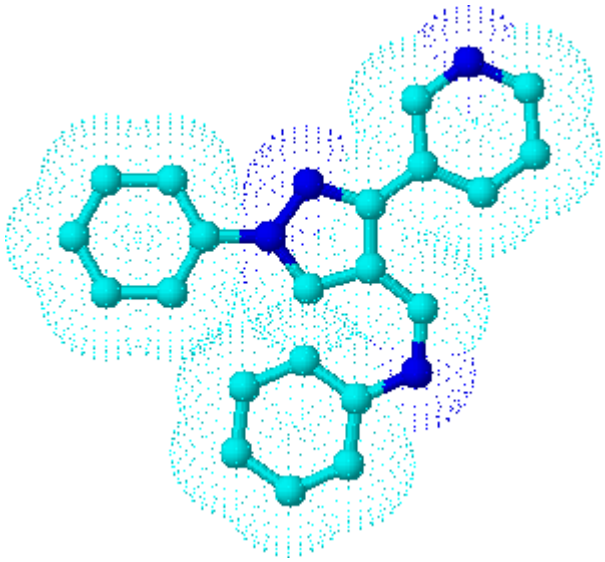
TABLE NO. 10a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC mg/ml*	*% Inhib*	*Activity*	*Comment*
RKP-43	295711	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	MIC Rifampin =
RKP-44	295712	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	0.25 mg/ml
RKP-45	295713	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	7	-	@ 98% Inhibition
RKP-46	295714	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-47	295715	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-48	295716	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	2	-	"
RKP-49	295717	3-Cl,4-F--C_6H_3-	Alamar	$H_{37}Rv$	>6.25	1	-	"
RKP-50	295718	3,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-51	295719	2,6-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	5	-	"
RKP-52	295720	2,4-$(CH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	6	-	"
RKP-53	295721	2,5-$(OCH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-54	295722	2-NO_2,4-$CH_3C_6H_3$-	Alamar	$H_{37}Rv$	>6.25	1	-	"



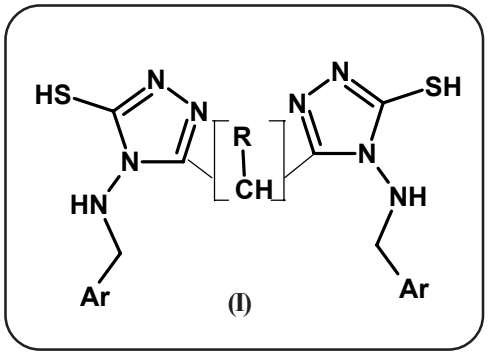
PART - IX

STUDIES ON

N-ARYL-1,N-PHENYL-3-β-PYRIDYL-PYRAZOL-4-YL-AZOMETHINE

INTRODUCTION

*A*zomethine derivatives have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activity. Azomethines are also known as Schiff's base and they are well known interemediate for the preparation of azetidinone, thiazolidinone, formazone, arylacetamide and many other derivatives. These are the compounds contain characteristic -C=N group. Holla, B. S. et. al.[524] have documented azomethine (I) having triazole moiety and possess good antibacterial activity.



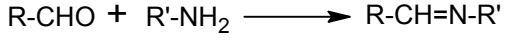
(I)

Azomethines are obtained mainly by warming the aldehyde & aromatic amine togethar. However, it is more convenient to work in a solvent such as alcohol, dilute acetic acid or glacial acetic acid. Some time the reaction is aided by traceof acid in other cases the hydrochloride of the amines can be used in the synthesis.

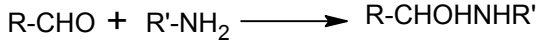
In general Schiff's bases do not react further with either of the reagents used in their preparation as do most of the other types of simple intermediates.

SYNTHETIC ASPECT :

1. General account of the summary of reaction of aldehydes with amine (aromatic or alipharic) has been reviewed by Murray.[525]



2. Strache[526] and Van Alphen[527] have prepared imine involves in two steps.
   a. Addition of the amine to the carbonyl group of the aldehyde gives aldol. The aldol is rerely capable of isolation.



b. The loss of water to give an imine (azomethine), this corresponds to the "crotonaldehyde stage" of the aldol condensation.

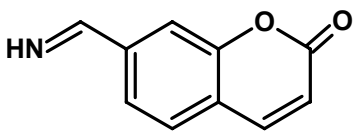
3. Oddo & Tognacchini[528] have introduced the comparative rates of formation of Schiff's base from aniline & substituted aniline & aromatic aldehyde using a cryscopic method follow the course of reaction.

Smalders, et. al.[529] synthesized some new azomethine to give potential antitumor reagent phosphonates. Yadawe M. S. and Patil S. A.[530] have synthesized azomethine derivative of type shown as below.

Mehta R. H. and et. al.[531] have synthesized coummarin schiff's base derivatives of type (II) and examined for their antibacterial activity.

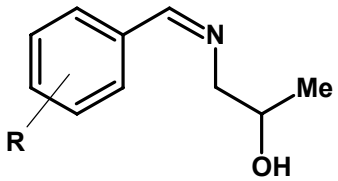
Khalafallah A. K. and Hassan M. E.[532] have prepared some styryl Schiff's bases spiro derivatives as potential antibacterial and antifungal activity. Sharaf El-Din, and Nabaweyal[533] have synthesized some azomethine derivatives (III) having good antibacterial activity.

$$R\text{-}CHOHNHR' \longrightarrow R\text{-}CH{=}N\text{-}R' + H_2O$$



(II)

R = Ph, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 2-Cl-C_6H_4CONH

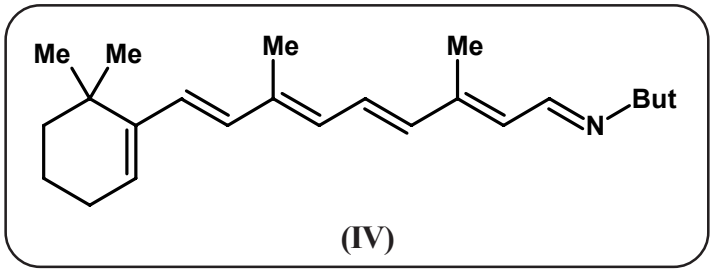


(III)

R = 3,4 -OH, 3, 4-NO_2 3,4-$(OMe)_2$

Chohan et. al.[534] have synthesized azomethines, which have been screened and compared for their antibacterial action against bacterial species Escherichia coli, Pesudomonus aeruginoase and Klebisella pneumoniase.

Das Joydip & Singh, Anilk[535] have synthesized azomethine shown as below.



(IV)

All-trans-N-refinylidene-n-butylamine (IV) can be stabillized in liposomes of phophatidylcholine. The rate of formation of the Schiff's base is found to decrease with increasing cholesteral concentration in the membrane.

Deshmukh M. D. and Doshi A. G.[536] prepared some new Schiff's bases show good antimicrobial activity against test organism S. aureus, E. coli, Saigella dysenteridse and salmonella typhi.

Wang, Yangang; Ye, Wenta; Yang, Jun;Lou,Aihony[537]havesynthesize dazomethines having good plant hormone activity. Das Arima et. al.[538] have prepared Schiff's bases of aminohydroxy guanidine (SB-AHG5) were tested for antiviral activity against herper simplex virus type I (HSV-1) and adenovirus type-5 (Ad-5) alone with 11 other heterocyclic SB-AHG5 some compounds has good antiadenoviral activity.

Solankee Anjani; Mistry, Pankaj; Patel V. M.[539] have synthesized some new Schiff's bases having good antibacterial activity.

Ram, Tilak et. al.[540] have synthesized some Schiff's bases, thiazolidinones 4-triazolines, and formazones of 2-chloro phenothiazines and screened against carrageenin-induced edema in albino rats. The thiazolidinones showed promising antiinflammatory activity.

Ali, yousif et. al.[541] have synthesized some Schiff's base derivatives of glucose contg. acetylenic bond were also prepared Hydroxybenzaldehydes were first converted to o-prop-2-ynyl-benzaldehydes followed by their condensation with glucosamine. The prepared Schiff base were tested for their bactericidal activity against E. coli and staphylococcus aureus.

Cascaval Alexandru; et. al.[542] have synthesized azomethines, which have good analgesic and antipyratic properties. Pandeya S. N. et. al.[543] have synthesized Schiff bases showed good activity against vibrio cholerae non-o., shigella boydii, Enterococcus faecalis and Edwaredsiella torla with mic in the rang of 10-25 µg/ml. Some compounds were found to be active against salmonellalyphi and vibro cholerae-0, (mic 25-150 µg/ml).

Omar and et. al.[544] have determined cyclocondensation of azomethines having good antischistosomal activity.

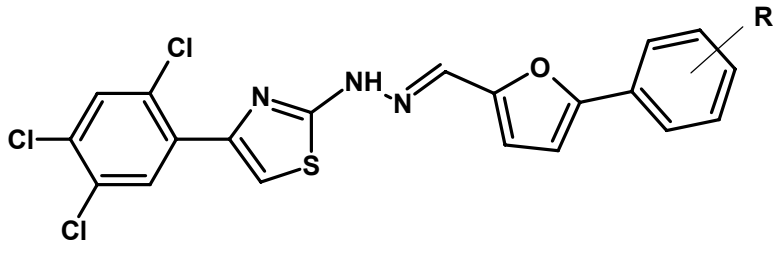
Pawar R. P. et. al.[545] have synthesized azomethines by the condensation of iodovanillin with different substituted aromatic amines. The good antibacterial activity was determined.

Chohan and co-workers[546] have synthesized a novel class of acetyl ferrocene derived Schiff bases possess antimicrobial activity.

Ergenc and co-workers[547]have synthesised azomethine derivatives having antifungal activity.

Holla B. S. et. al.[548] have prepared mannich bases. Pandey, Taruna et. al.[549] prepared azomethines and their boron complexes and screened for their antifungal and antibacterial properties. It is evident that azomethines alone were quite toxic but their activity increased after complexation.

Yadav Bodke & S. S. Sangapure[550] have synthesised some azomethines and tested for their biological activity. B. Shivarama Holla et. al.[551] have prepared some new Schiff's bases having anticancer activity. Ravindra V. Chambhare et. al.[552] have prepared some azomethines of type and tested for their antimicrobial activity. B. Shivarama Holla., et. al.[553] have synthesized azomethines of type (V) having antibacterial and anti-inflammatory activity.



(V) **R=2-NO_2, 4-NO_2, 4-Br,.....etc.**

Looking to the interesting properties of azomethines, we have synthesised some new azomethines, which have been described as under.

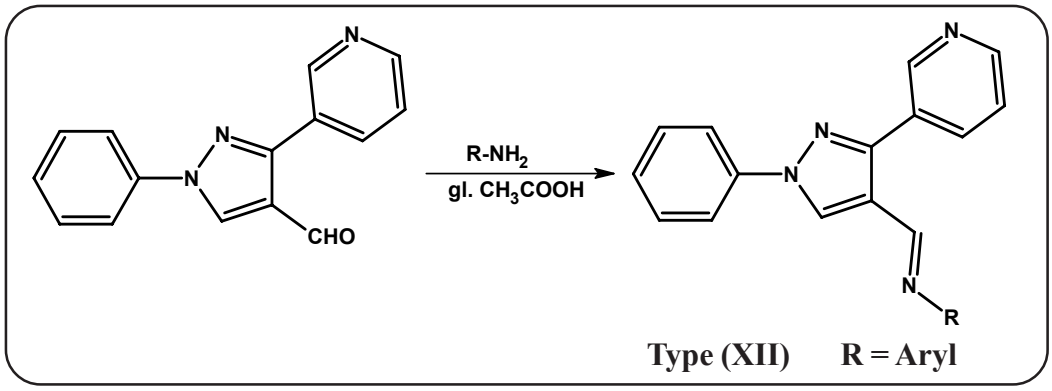
SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF N-ARYL-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINE

SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-ARYLAMINOMETHYL-3-â-PYRIDYL-1,N-PHENYLPYRAZOLE

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF N-ARYL-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINES

The growing patent literature of recent years demonstrates that the azomethine derivatives are used as better therapeutic agents. In view of these findings, it appeared of interest to synthesise Schiff's base of the type (XII) by the condensation of 1,N-Phenyl-3-â-pyridyl-4-formyl pyrazole with various aromatic amines in order to study their biodynamic behavior.

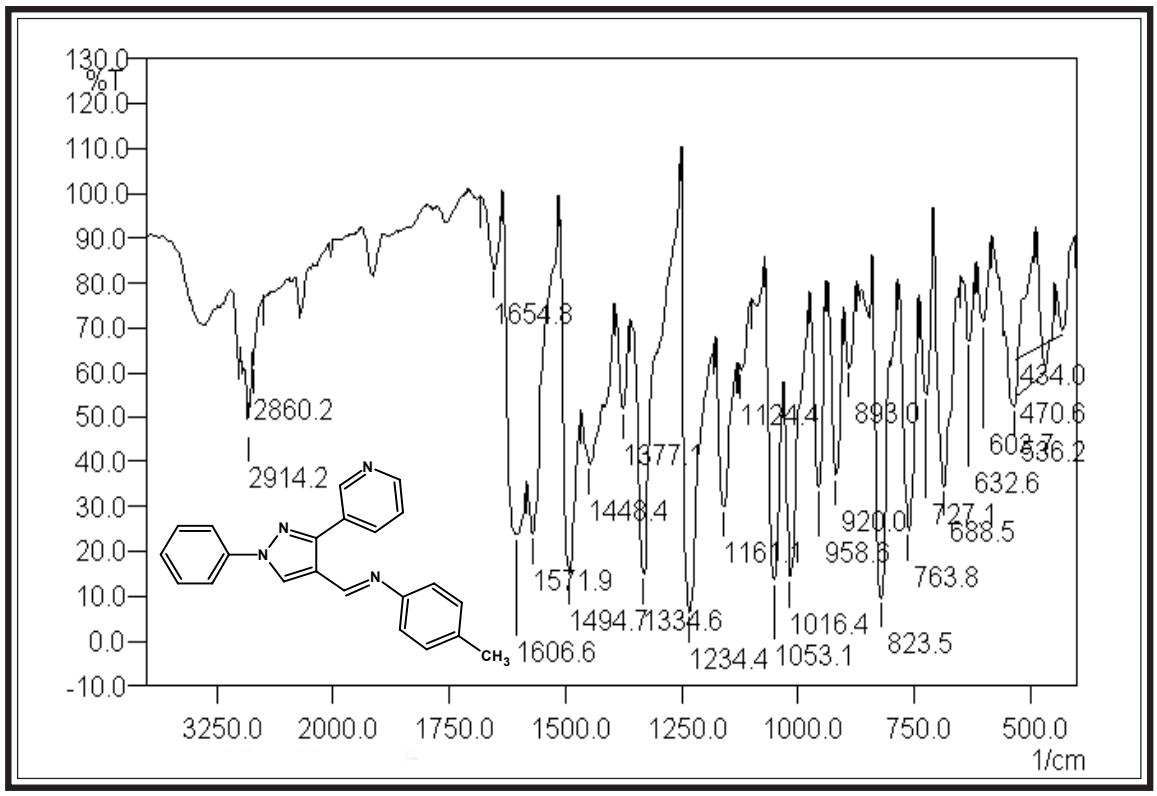


Type (XII) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. The mass spectra of N-(p-Tolyl)-1,N-phenyl -3-â-pyridyl-pyrazol-4-yl-azomethine give m/z = 337 (recorded on Page No.174). The fragmentation is also explained (Page No. 175).

The products have been screened for their *in vitro* biological assay like antimicrobial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

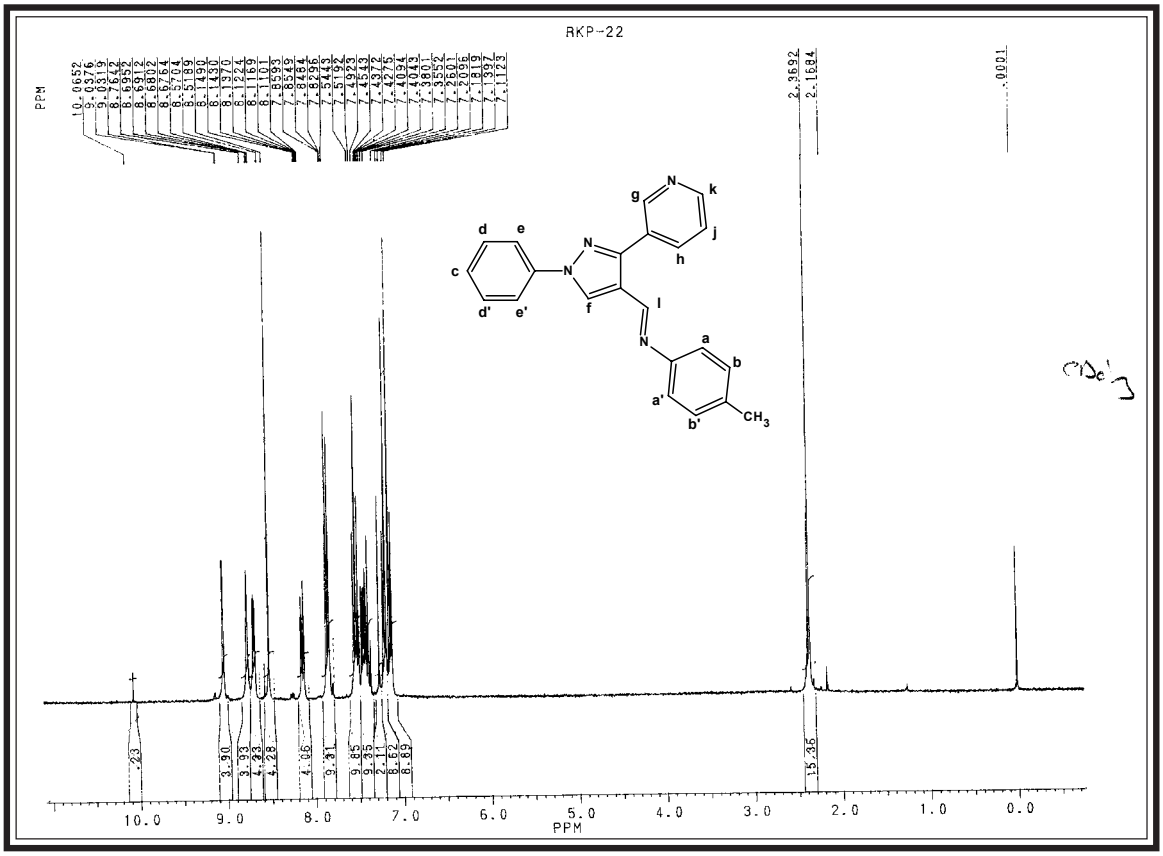
IR SPECTRAL STUDY OF N-(p-TOLYL)-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2914	2975–2920	95
$-CH_3$	C – H str. (sym.)	2860	2880–2860	"
	C – H i.p. (def.)	1448	1470-1435	"
	C – H o.o.p. (def.)	1377	1395–1370	"
Aromatic	C – H str.	3072	3090–3030	96
	C – C str.	1571	1585-1570	
	C – H i.p. (def.)	1124	1125–1090	"
	C – H o.o.p (def.)	823	835–810	"
Pyrazole	C = N str.	1571	1610–1590	96
moety	C – N str.	1234	1230–1220	"
Schiff Base	C = N str.	1606	1660-1580	"

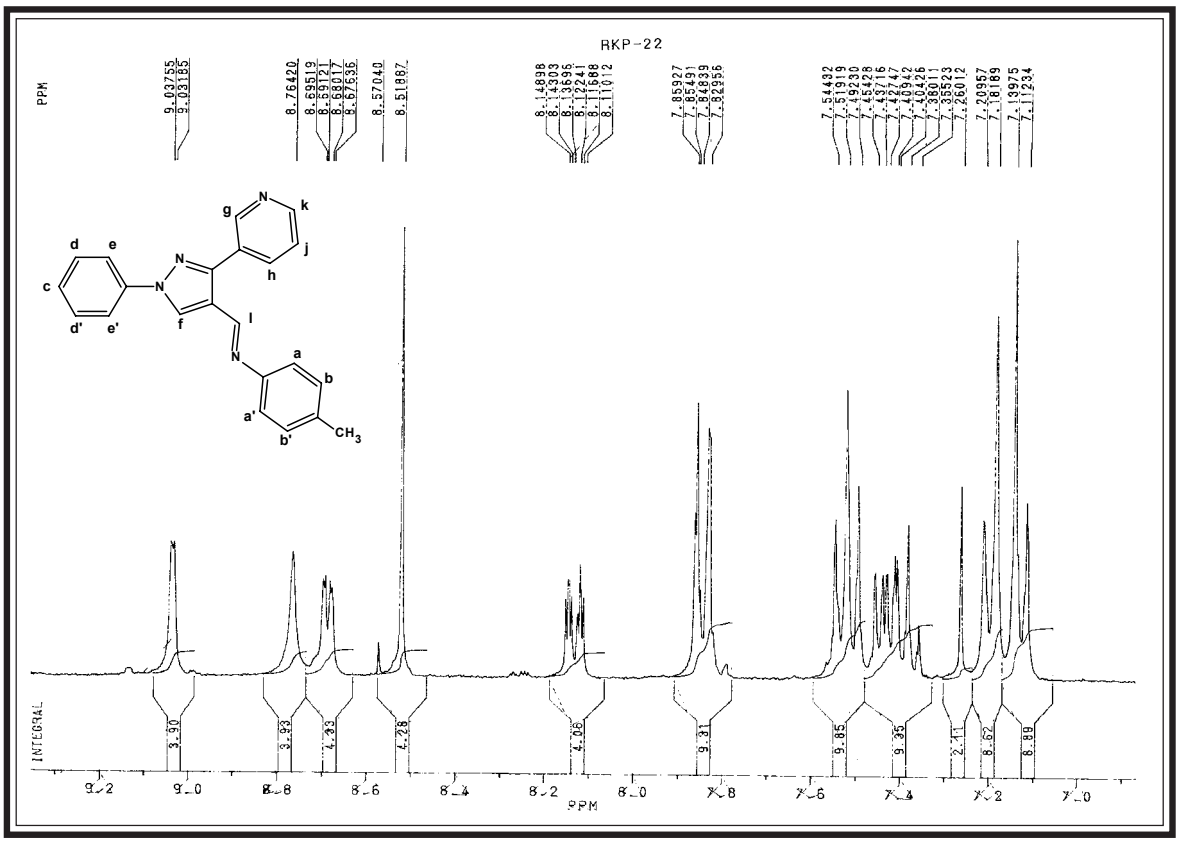
PMR SPECTRAL STUDY OF N-(p-TOLYL)-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINE

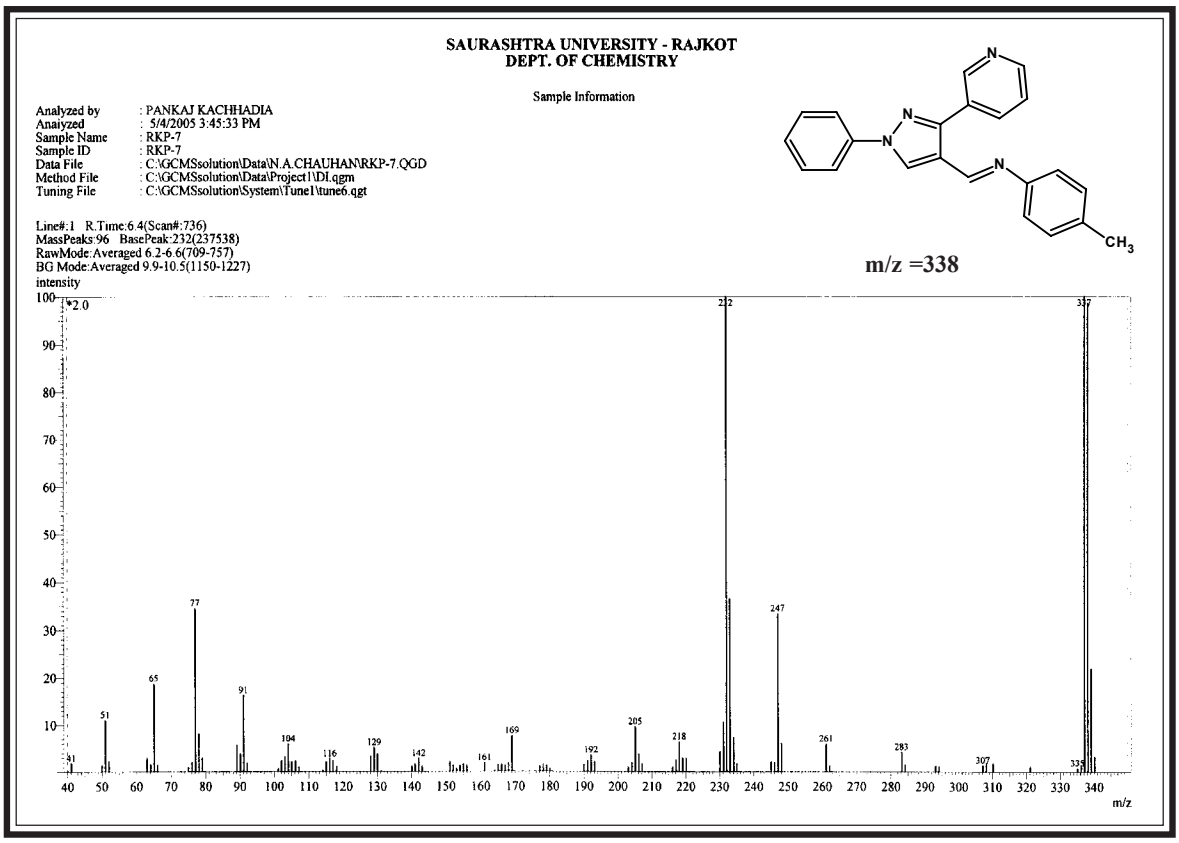


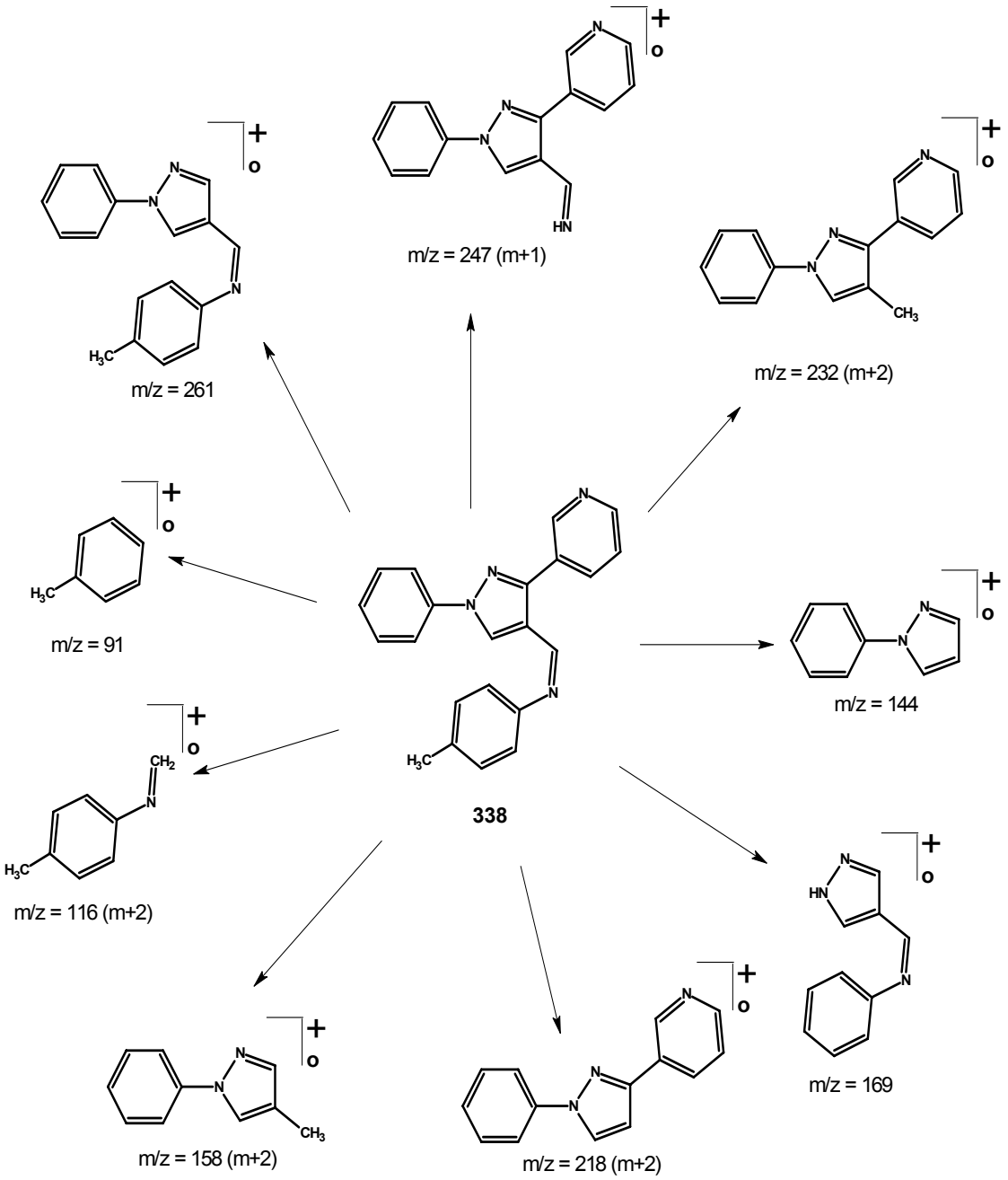
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.36	3H	singlet	Ar-CH_3	-
2	7.11-7.14	2H	doublet	Ar-Haa’	Jaa’=8.2
3	7.18-7.21	2H	doublet	Ar-Hbb’	Jbb’=8.3
4	7.35-7.45	1H	multiplet	Ar-Hh	-
5	7.49-7.54	3H	triplet	Ar-Hc,d,d’	-
6	7.82-7.85	2H	doublet	Ar-Hee’	Jee’=8.9
7	8.11-8.14	1H	multiplet	Ar-Hj	-
8	8.51	1H	singlet	Ar-Hf	-
9	8.67-8.70	1H	d,d	Ar-Hk	Jkj=6 Jkh=1.2
10	8.76	1H	singlet	Ar-Hl	-
11	9.03	1H	singlet	Ar-Hg	-

EXPANDED AROMATIC REGION






m/z = 247 (m+1)
m/z = 261
m/z = 232 (m+2)
m/z = 91
m/z = 144
338
m/z = 116 (m+2)
m/z = 169
m/z = 158 (m+2)
m/z = 218 (m+2)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF N-ARYL-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINES

[A] Synthesis of 3-Acetylpyridine phenyl hydrazone

See, Part-I, Section-I (A).

[B] Synthesis of 1N-Phenyl-3-â-pyridyl-4-fromyl pyrazole

See, Part-I, Section-I (B).

[C] Synthesis of N-(p-Tolyl)-1,N-phenyl -3-â-pyridyl-pyrazol-4-yl-azomethine

A mixture of 1N-Phenyl-3-β-pyridyl-4-formyl-pyrazole (2.65g, 0.01M) and p-toludine dissolved in ethanol (20 ml) was refluxed in ethanol (95%) for 6 hrs. gl.acetic acid is used as catalyst. The contents were cooled and product isolated was crystallised from ethanol. Yield, 75%, m.p. 222^{o}C ($C_{22}H_{18}N_4$; Found : C, 78.03%; H, 5.31%; N, 16.53%; Requires : C, 78.08%; H, 5.36%; N, 15.56%).

Similarly, other nitriles were prepared. The physical constants are recorded in Table No. 11.

[D] Antimicrobial activity of N-aryl-1,N-phenyl -3-â-pyridyl-pyrazol-4-yl-azomethines

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solution are recorded in Graphical Chart No. 11.

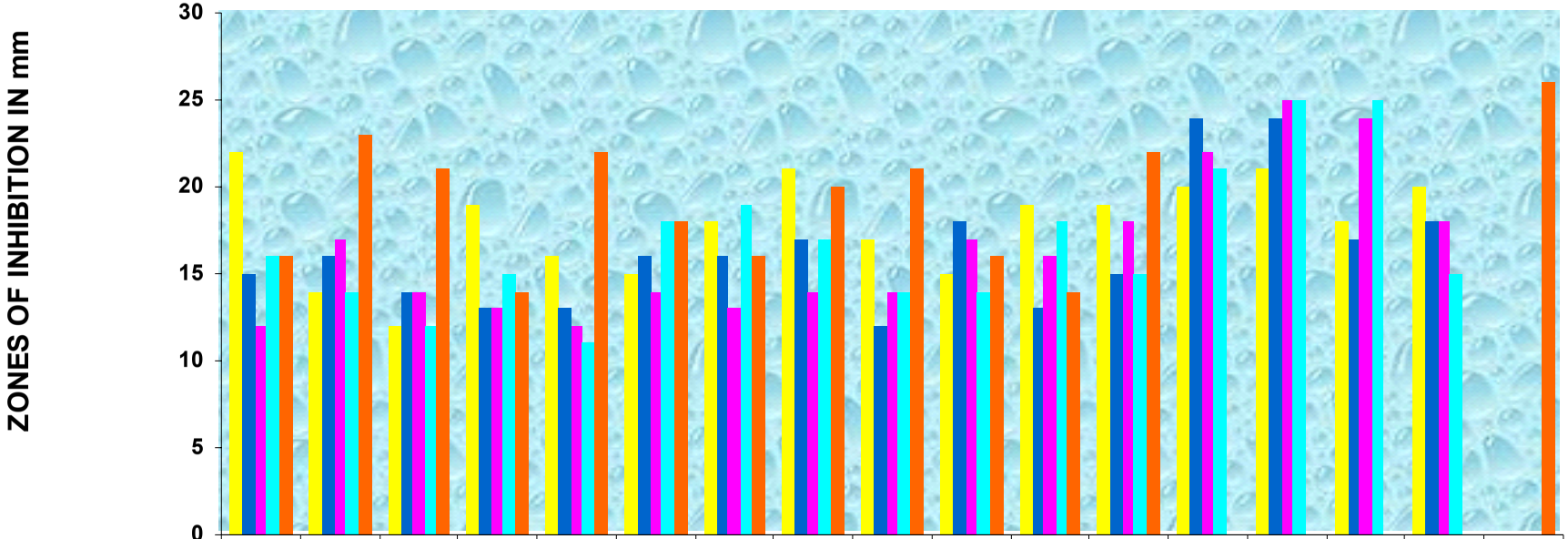
TABLE NO. 11 : PHYSICAL CONSTANTS OF N-ARYL-1,N-PHENYL-3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
11a	2-CH_3-C_6H_4-	$C_{22}H_{18}N_4$	338	194	0.60	70	16.56	16.53
11b	4-CH_3-C_6H_4-	$C_{22}H_{18}N_4$	338	222	0.58	75	16.56	16.55
11c	2-OCH_3-C_6H_4-	$C_{22}H_{18}N_4O$	354	207	0.51	67	15.81	15.79
11d	3-OCH_3-C_6H_4-	$C_{22}H_{18}N_4O$	354	186	0.57	55	15.81	15.78
11e	4-OCH_3-C_6H_4-	$C_{22}H_{18}N_4O$	354	178	0.52	72	15.81	15.80
11f	3-Cl-C_6H_4-	$C_{21}H_{15}ClN_4$	358.5	167	0.49	52	15.61	15.58
11g	4-Cl-C_6H_4-	$C_{21}H_{15}ClN_4$	358.5	201	0.60	63	15.61	15.59
11h	2-F-C_6H_4-	$C_{21}H_{15}FN_4$	342	236	0.43	57	16.36	16.33
11i	4-F-C_6H_4-	$C_{21}H_{15}FN_4$	342	190	0.39	61	16.36	16.35
11j	4-Br-C_6H_4-	$C_{21}H_{15}BrN_4$	403	229	0.58	50	13.89	13.87
11k	4-NO_2-C_6H_4-	$C_{21}H_{15}Cl_2N_5O_2$	369	163	0.60	58	18.96	18.92
11l	2,4-$(CH_3)_2$-C_6H_3	$C_{23}H_{20}N_4$	352	172	0.52	62	15.90	15.87

*TLC Solvent System : Acetone : Benzene

3 : 7

GRAPHICAL CHART NO. 11 : ANTIMICROBICAL ACTIVITY OF N-ARYL-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINES



	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	22	14	12	19	16	15	18	21	17	15	19	19	20	21	18	20	0
B. subtillus	15	16	14	13	13	16	16	17	12	18	13	15	24	24	17	18	0
E.coli	12	17	14	13	12	14	13	14	14	17	16	18	22	25	24	18	0
P. vulgaris	16	14	12	15	11	18	19	17	14	14	18	15	21	25	25	15	0
A. niger	16	23	21	14	22	18	16	20	21	16	14	22	0	0	0	0	26

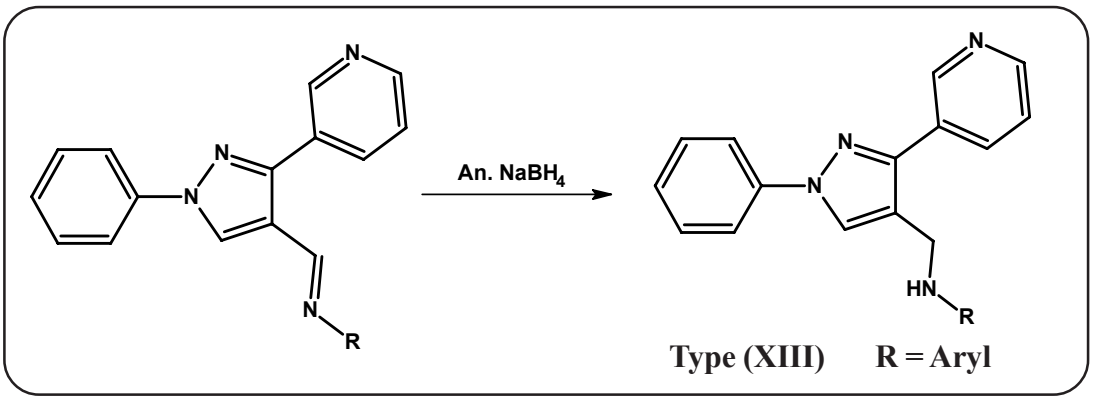
BIOLOGICAL EVALUATION OF N-ARYL-1,N-PHENYL -3-â-PYRIDYL-PYRAZOL-4-YL-AZOMETHINES

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
11a(22)	11j(18)	11l(18)	11g(19)	11b(23)
11h(21)	11h(17)		11f(18)	11e(22)
11d(19)			11k(18)	11l(22)
11k(19)			11h(17)	11c(21)
11l(19)			11a(16)	11i(21)
			11d(15)	
			11l(15)	
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

SECTION-II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-ARYLAMINOMETHYL-3-â-PYRIDYL-1,N-PHENYLPYRAZOLE

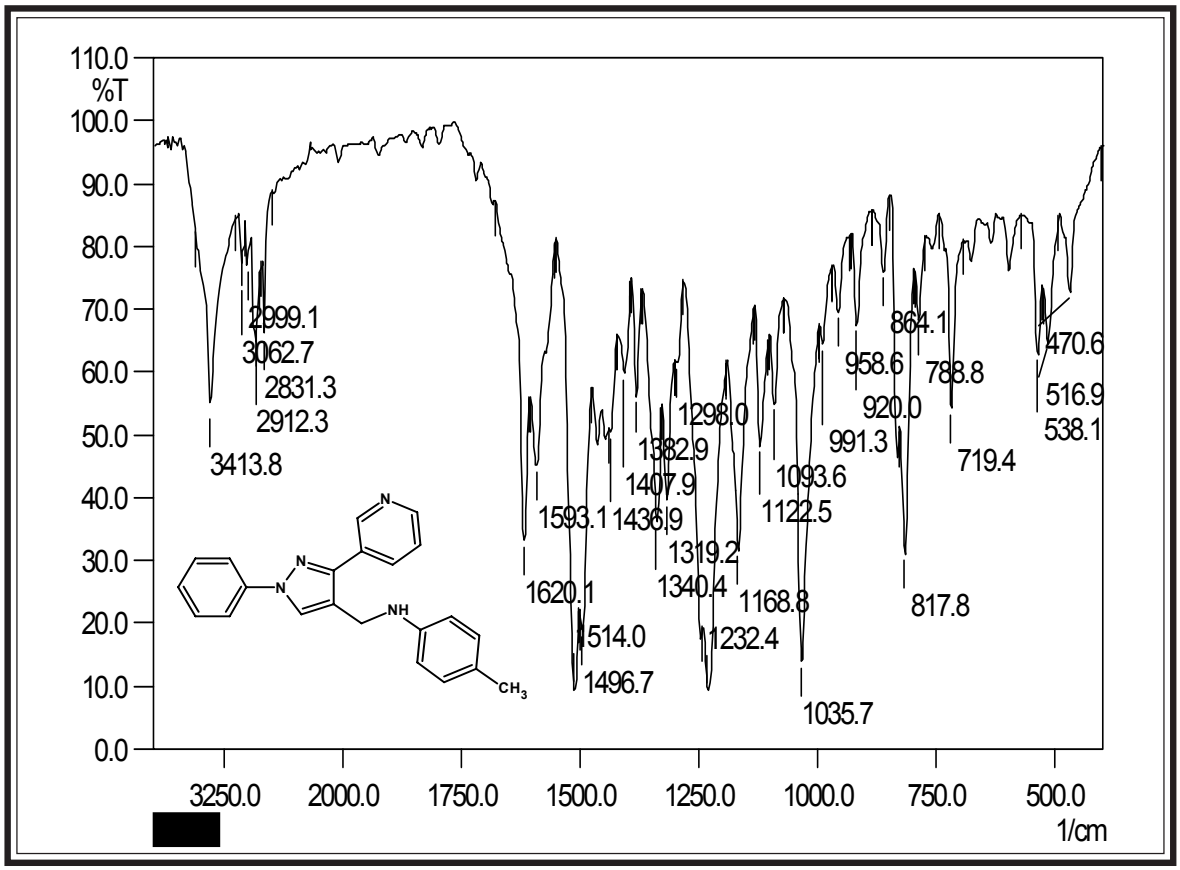
Aminomethyl derivatives of heterocyclic compounds are associated with diverse biological activity. These finding prompted us to synthesise some representative aminomethyl derivative of type (I) bearing pyrazole moiety obtained by selective reduction of (imine group) of Schiff's bases of type (XII) with sodium borohydride in controlled experimental condition as shown in the reaction scheme.



The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. The mass spectra of 4-p-Tolyl-aminomethyl-3-â-pyridyl-1,N-phenylpyrazole give m/z = 340 (recorded on Page No. 183). The fragmentation is also explained (Page No. 184).

The products have been screened for their *in vitro* biological assay like antimicrobial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

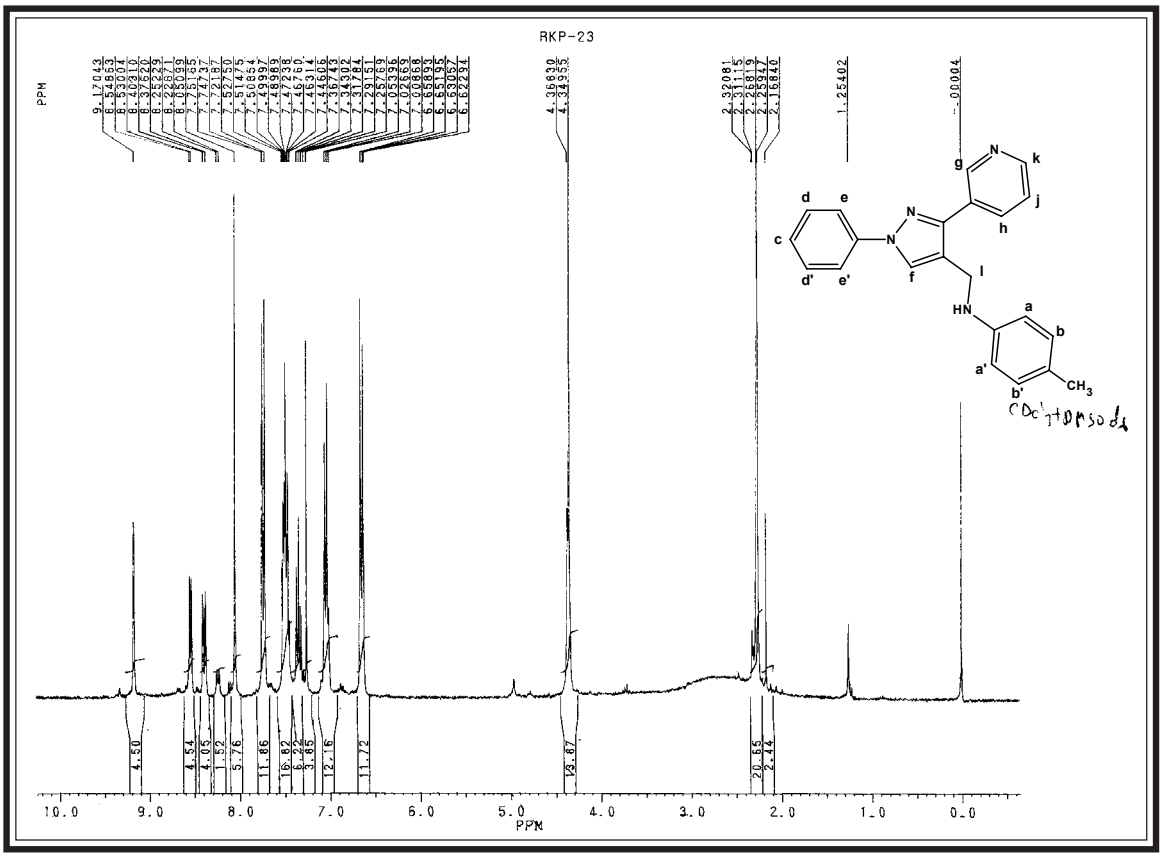
IR SPECTRAL STUDY OF 4-(p-TOLYL)-AMINOMETHYL-3-â-PYRIDYL-1N-PHENYLPYRAZOLE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2912	2975–2920	95
$-CH_3$	C – H str. (sym.)	2831	2880–2860	"
	C – H i.p. (def.)	1407	1470–1405	"
	C – H o.o.p. (def.)	1382	1395–1370	"
Alkane	C – H str.(asym.)	2912	2936-2916	"
$-CH_2$	C – H def.	1496	1485-1445	"
Aromatic	C – H str.	3062	3090–3030	96
	C – C str.	1593	1585-1570	
	C – H i.p. (def.)	1168	1175–1090	"
	C – H o.o.p (def.)	817	835–810	"
Pyrazole	C = N str.	1571	1610–1590	96
moety	C – N str.	1234	1230–1220	"

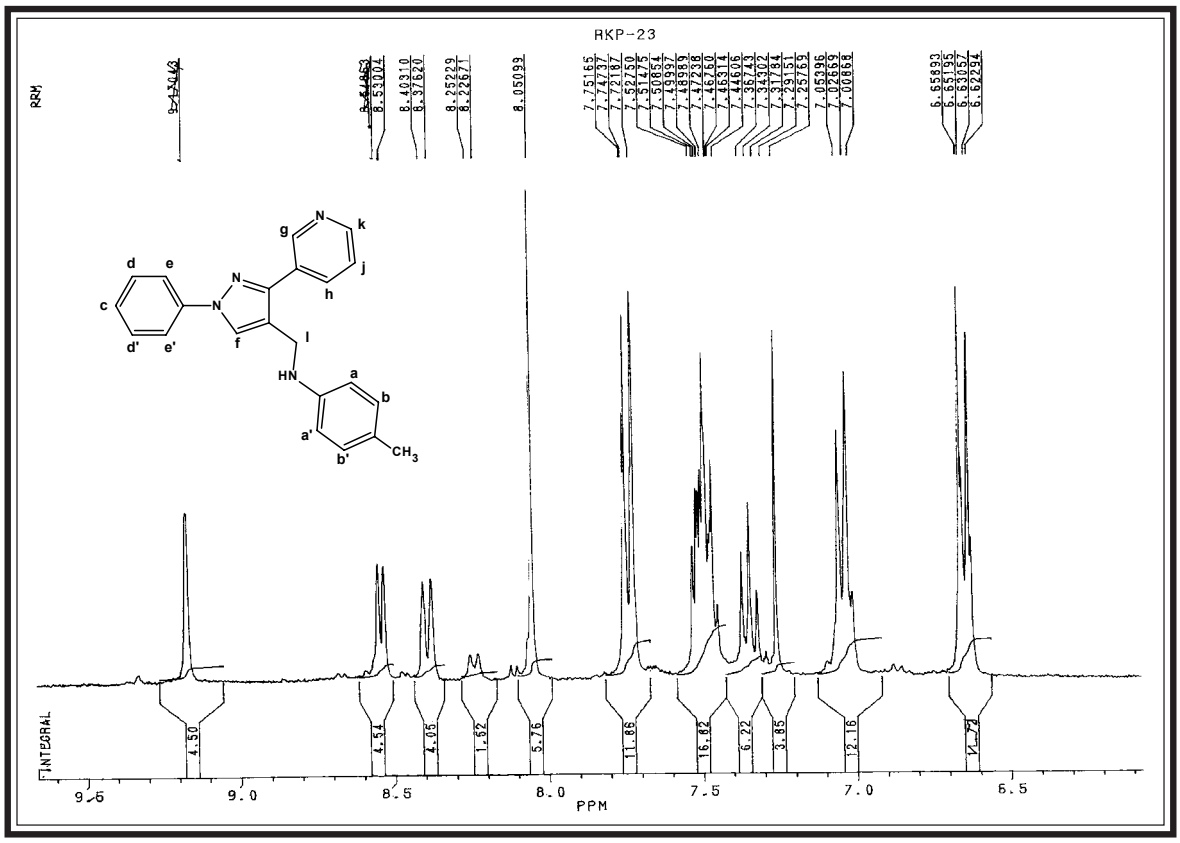
PMR SPECTRAL STUDY OF 4-(p-TOLYL)-AMINOMETHYLENE-3-â-PYRIDYL-1N-PHENYLPYRAZOLE

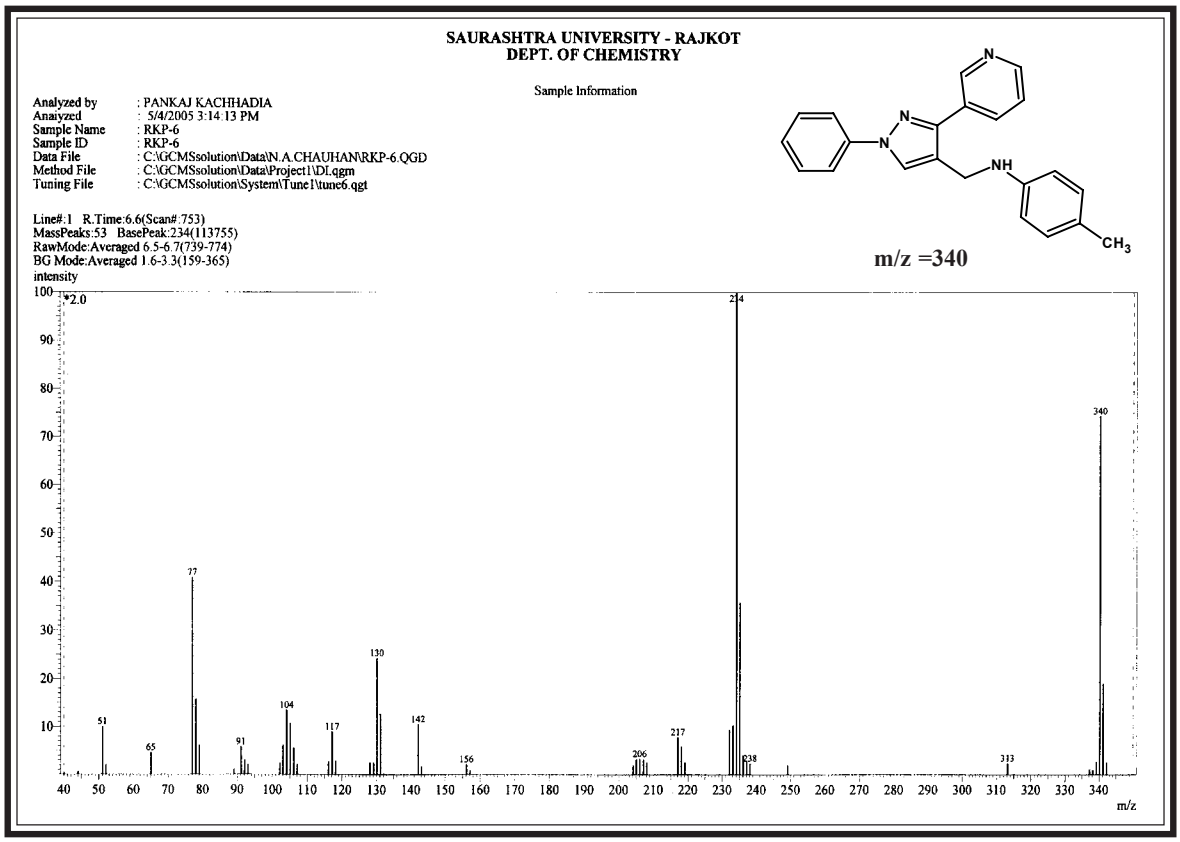


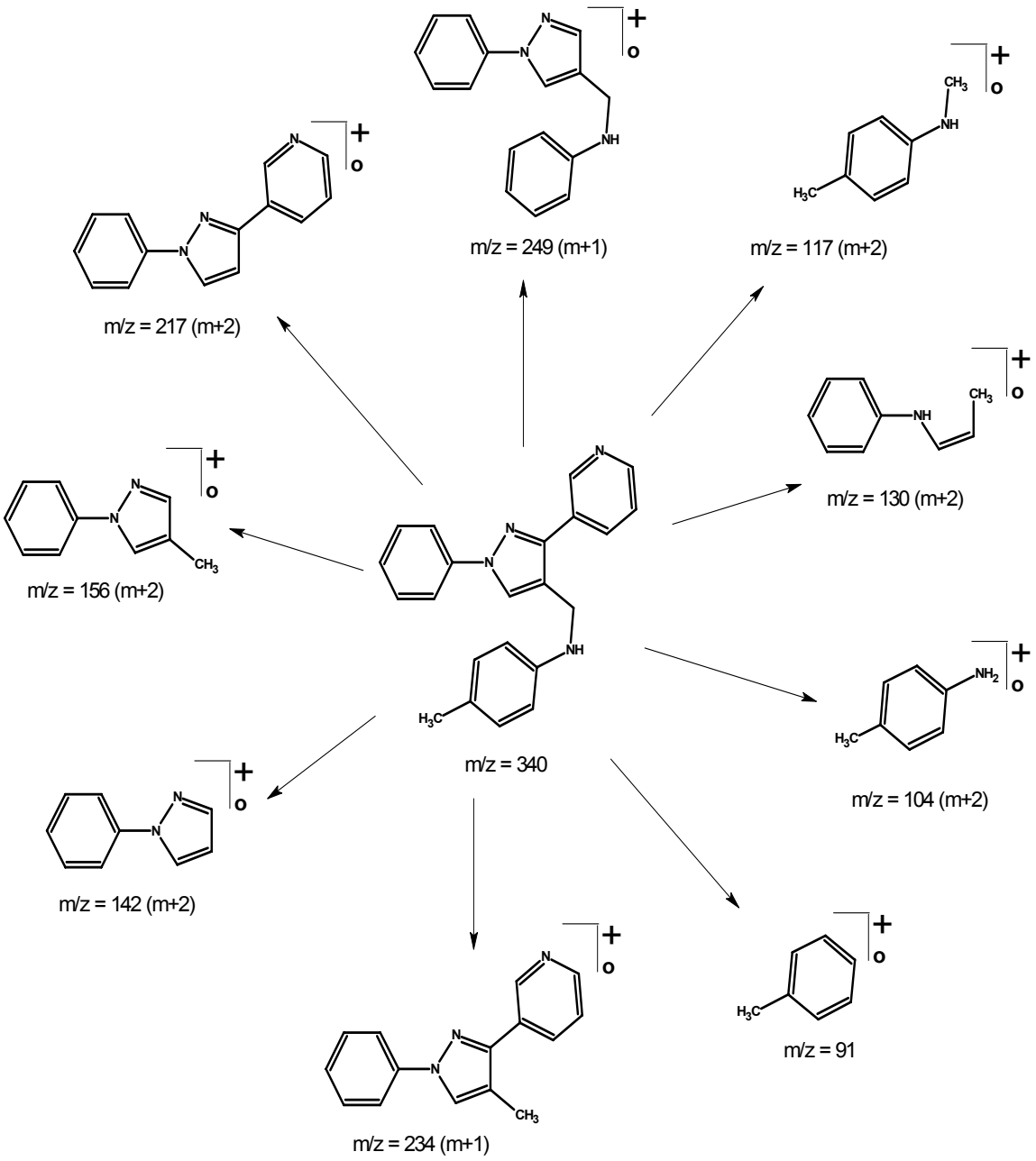
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.26	3H	singlet	Ar-CH_3	-
2	4.34	2H	singlet	-CH_2(A_1&A_2)	-
3	6.62-6.65	2H	doublet	Ar-Haa'	Jaa'=8.5
4	7.02-7.05	2H	doublet	Ar-Hbb'	Jbb'=8.2
5	7.31-7.36	1H	triplet	Ar-Hj	Jjk=7.6 Jjh=7.3
6	7.46-7.49	2H	doublet	Ar-Hdd'	Jdd'=8.3
7	7.49-7.52	1H	multiplet	Ar-Hc	-
8	7.72-7.75	2H	doublet	Ar-Hee'	Jee'=8.9
9	8.05	1H	singlet	Ar-Hf	-
10	8.37-8.40	1H	doublet	Ar-Hk	Jkj=8.1
11	8.53-8.56	1H	doublet	Ar-Hh	Jhj=6.0
12	9.10	1H	singlet	Ar-Hg	-

EXPANDED AROMATIC REGION






m/z = 249 (m+1)
m/z = 217 (m+2)
m/z = 117 (m+2)
m/z = 156 (m+2)
m/z = 130 (m+2)
m/z = 340
m/z = 142 (m+2)
m/z = 104 (m+2)
m/z = 234 (m+1)
m/z = 91

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-ARYLAMINOMETHYL-3-â-PYRIDYL-1,N-PHENYLPYRAZOLES

[A] Synthesis of 3-Acetyl pyridine phenyl hydrazone

See, Part-I, Section-I (A).

[B] Synthesis of 1N-Phenyl-3-â-pyridyl-4-fromyl pyrazole

See, Part-I, Section-I (B).

[C] Synthesis of 4-Arylaminomethyl-3-â-pyridyl-1N-phenylpyrazole

Sodium borohydride (0.15M, 0.57g) was added to a methanolic solution of 4-(p-Tolyl)amino methyl-3-β-pyridyl-1,N-phenyl pyrazole (0.01M, 3.38 g) over a period of 30 minutes at temperature 5-10^{o}C. The reaction mixture then kept over night at room temp. The excess borohydride was neutralized by adding water and the product was extracted with ether. The ether extract was washed with water untill neutral, then dried over anhydrous Na_2SO_4 and finally the ether was evaportated to give aminomethyl derivatives. Yield, 60%, m.p. 136^{o}C ($C_{22}H_{20}N_4$; Found : C, 77.59%; H, 5.90%; N, 16.44%; Requires : C, 77.62%; H, 5.92%; N, 16.46%).

Similarly, other nitriles were prepared. The physical constants are recorded in Table No. 12.

[D] Antimicrobial activity of 4-Arylaminomethyl-3-â-pyridyl-1,N-phenylpyrazoles

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solution are recorded in Graphical Chart No. 12.

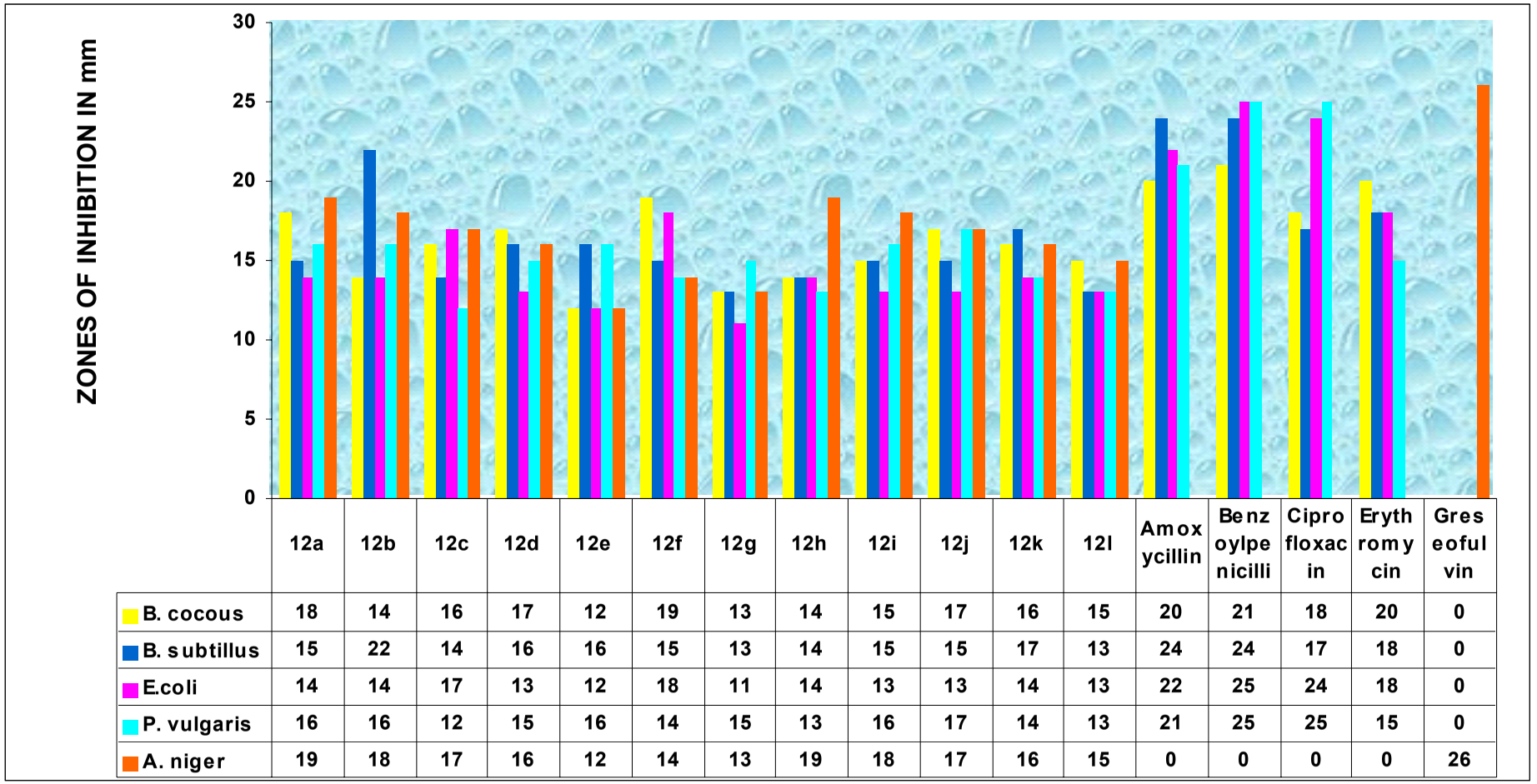
TABLE NO. 12 : PHYSICAL CONSTANTS OF 4-ARYLAMINOMETHYL-3-â-PYRIDYL-1,N-PHENYLPYRAZOLES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
12a	2-CH_3-C_6H_4-	$C_{22}H_{20}N_4$	340	194	0.67	52	16.46	16.42
12b	4-CH_3-C_6H_4-	$C_{22}H_{20}N_4$	340	222	0.63	60	16.46	16.44
12c	2-OCH_3-C_6H_4-	$C_{22}H_{18}N_4O$	356	207	0.55	45	15.72	15.70
12d	3-OCH_3-C_6H_4-	$C_{22}H_{18}N_4O$	356	186	0.51	56	15.72	15.69
12e	4-OCH_3-C_6H_4-	$C_{22}H_{18}N_4O$	356	178	0.59	39	15.72	15.71
12f	3-Cl-C_6H_4-	$C_{21}H_{17}ClN_4$	360.5	167	0.47	42	15.53	15.51
12g	4-Cl-C_6H_4-	$C_{21}H_{17}ClN_4$	360.5	201	0.52	54	15.53	15.80
12h	2-F-C_6H_4-	$C_{21}H_{17}FN_4$	344	236	0.49	40	16.27	16.24
12i	4-F-C_6H_4-	$C_{21}H_{17}FN_4$	344	190	0.44	48	16.27	16.25
12j	4-Br-C_6H_4-	$C_{21}H_{17}BrN_4$	405	229	0.50	51	13.82	13.79
12k	4-NO_2-C_6H_4-	$C_{21}H_{17}Cl_2N_5O_2$	371	163	0.56	37	18.86	18.84
12l	2,4-$(CH_3)_2$-C_6H_3	$C_{23}H_{22}N_4$	354	172	0.60	45	15.81	15.79

*TLC Solvent System : Acetone : Benzene

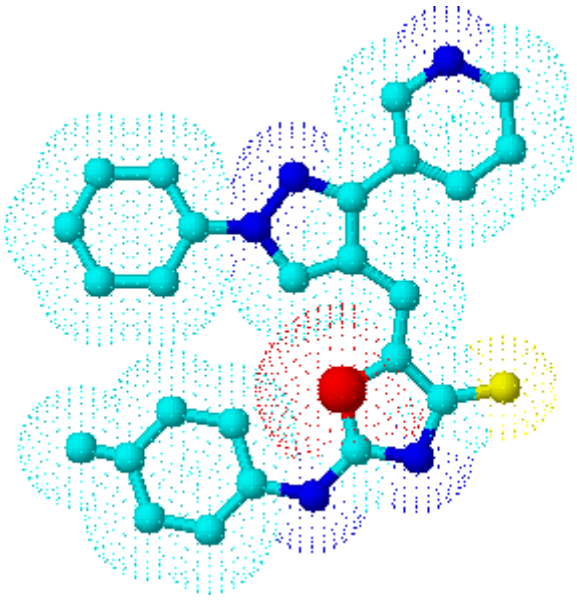
3 : 7

GRAPHICAL CHART NO. 12 : ANTIMICROBICAL ACTIVITY OF 4-ARYLAMINOMETHYL-3-â-PYRIDYL-1,N-PHENYLPYRAZOLES



	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	12k	12l	Amoxycillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	18	14	16	17	12	19	13	14	15	17	16	15	20	21	18	20	0
B. subtillus	15	22	14	16	16	15	13	14	15	15	17	13	24	24	17	18	0
E.coli	14	14	17	13	12	18	11	14	13	13	14	13	22	25	24	18	0
P. vulgaris	16	16	12	15	16	14	15	13	16	17	14	13	21	25	25	15	0
A. niger	19	18	17	16	12	14	13	19	18	17	16	15	0	0	0	0	26

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	***B. subtillus***	***E. coli***	***P. vulgaris***	***A. niger***
1	**2**	**3**	**4**	**5**
12f(19)	12b(18)	12f(18)	12j(17)	12a(19)
12a(18)	12k(17)		12a(16)	12h(19)
			12b(16)	
			12e(16)	
			12i(16)	
			12d(15)	
			12l(15)	
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	



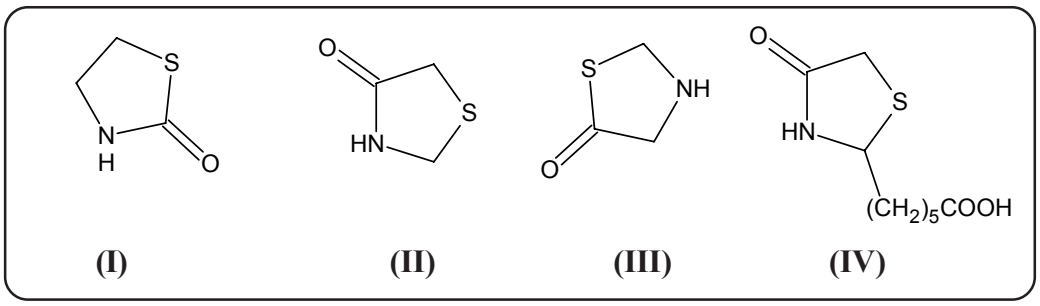
PART - X

STUDIES ON

THIAZOLIDINONES

INTRODUCTION

Thiazolidinones, which belong to an important group of heterocyclic compounds have been extensively explored for their applications in the field of medicine. Thiazolidinones, with a carbonyl group at position 2 in structure (I) and position 4 or 5 in structure(II) have been subjected for extensive study in the recent past. Numerous reports have appeared in the literature which highlight their chemistry and use.



(I) **(II)** **(III)** **(IV)**

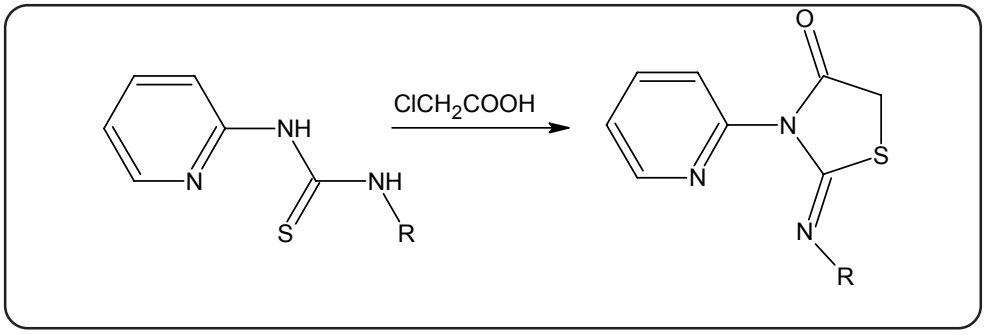
4-Thiazolidinones are derivatives of thiazolidine with carbonyl group at 4-position (II). Substituent in the 2, 3 and 5 positions may be varied, but the greatest different in structure and properties is exerted by the groups attached to carbon atom at the 2-position and to nitrogen atom at the 3-position. The cyclic structure was assigned after recognition of mercaptoacetic acid as a primary product of hydrolysis of 3-phenyl-2-phenylimino-4-thiazolidinones.[554]

A well known antibiotic, actithiazic acid (IV), isolated from a species of streptomyces shows specific *in vitro* activity against *M. tuberculosis*, but it is inactive *in vivo* probably due to antagonisation by biotin, bears the 4-thiazolidinone skeleton

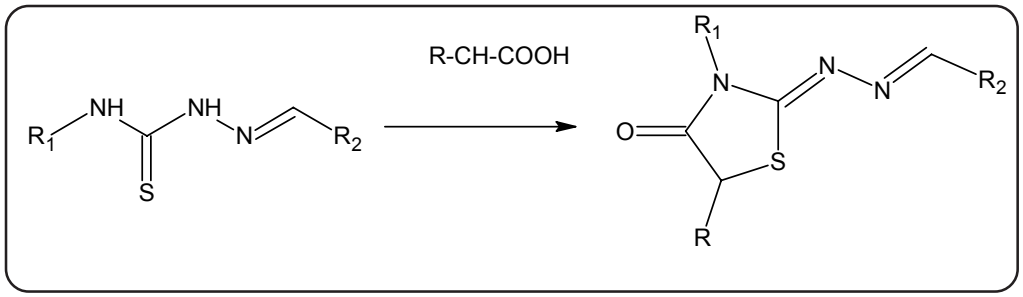
SYNTHETIC ASPECT

Several methods for the preparation of 4-thiazolidinones are narrated in literature[555-563]

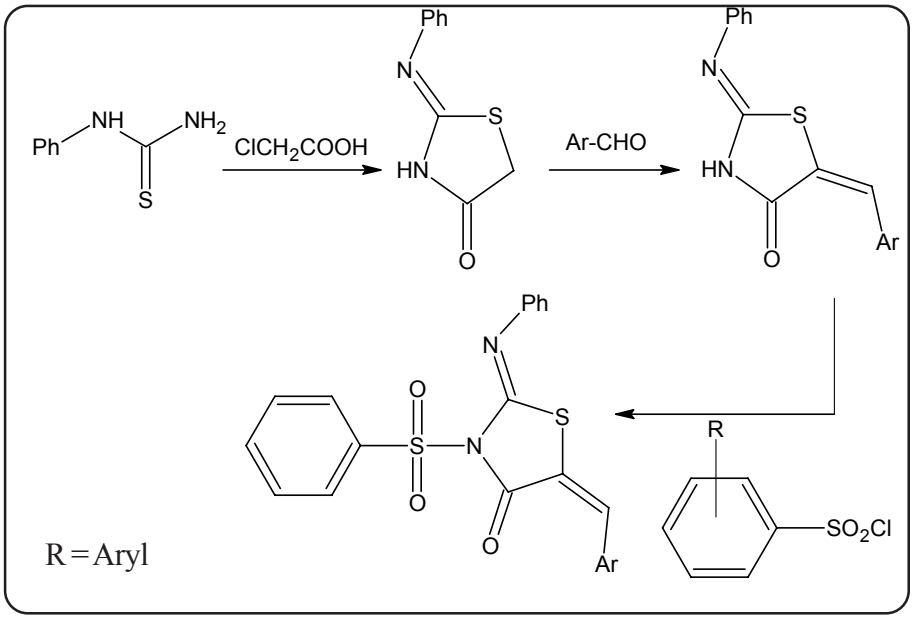
1. R. Nath and K. Shanker[564] have prepared 4-thiazolidinones by cyclization of N-aryl-N'-(2'-pyridyl)-thiocarbamide with chloroacetic acid.



2. I. D. Shah and J. P. Trivedi[565] have synthesized thiazolidinones from 4-aryl thiosemicarbazones by condensing them with chloroacetic acid, α-bromo propionic and α-bromophenyl acetic acid.

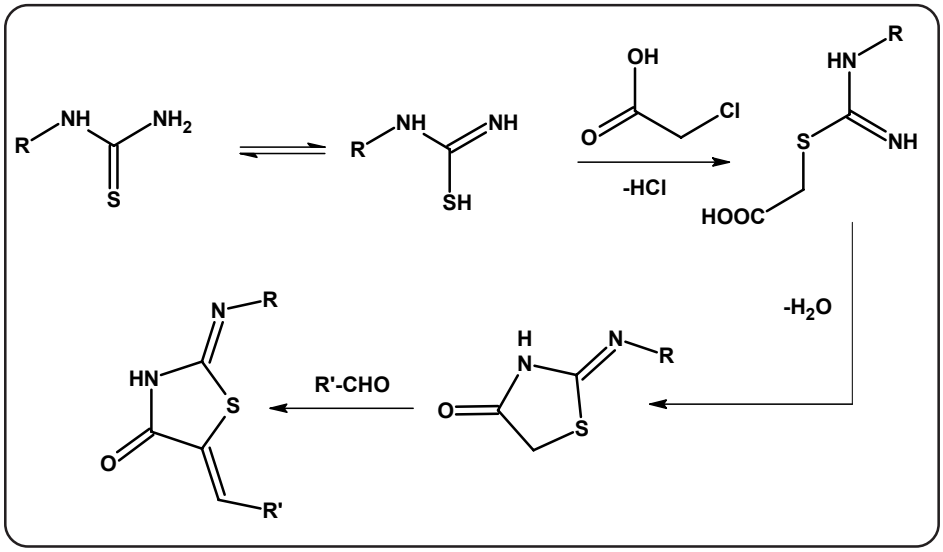


3. M. Seeda et. al.[566] have synthesized some new thiazolidinones.



MECHANISM

The reaction of 4-thiazolidinones proceeds by the attacks of the chloroacetic acid upon the C=S group, the tautomerism takes place with removal of HCl followed by removal of water and subsequent cyclization.



THERAPEUTIC IMPORTANCE

Much research has been carried out with the aim to finding therapeutic values of thiazolidinone moiety since their discovery. The thiazolidinones, substituted at 2 and 3 position are reported to exhibit a wide variety of biological activities.

1. Antibacterial[567,568]
2. Antitubercular[569,570]
3. Anti HIV and anticancer[571]
4. Antidiabetic[572]
5. Insecticidal[573]
6. Herbicidal[574]
7. Anthelmintics[575,576]
8. Cardiovascular[577]
9. Mosquito repellent[578]
10. Antiviral[579]
11. Hypnotic[580-582]
12. Antifungal[583-585]
13. Antitumor[586]

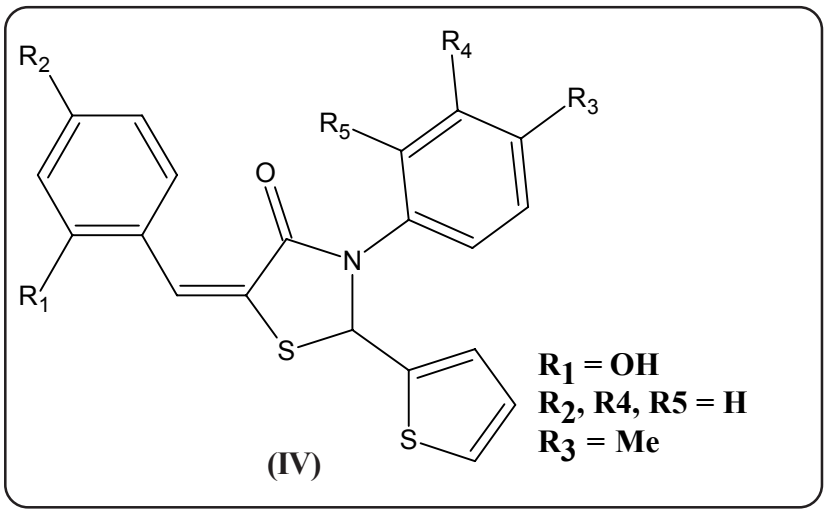
14. Antiulcer[587,588]

15. Local anaesthetic[589]

16. Antimicrobial[590,591]

Pawar and co-workers[592] reported synthesis and *in vitro* antibacterial activity of some 4-thiazolidinone derivatives. Goel et. al.[593] have synthesized thiazolidinone derivatives and compared their antiinflammatory activity, ulcerogenic liability, cardiovascular and CNS effects. In other study, some thiazolidinones have been found to be promising antibacterial agent.[594,595]

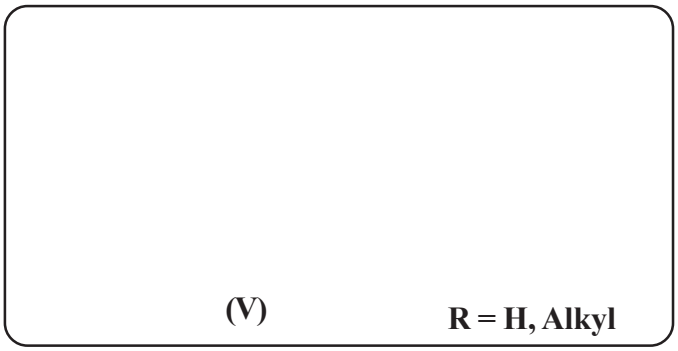
Siddique, Mohammed et. al.[596] have prepared substituted thiazolidinones (IV) and reported their antibacterial, antifungal, antithyroid and amoebicidal properties.



(IV)

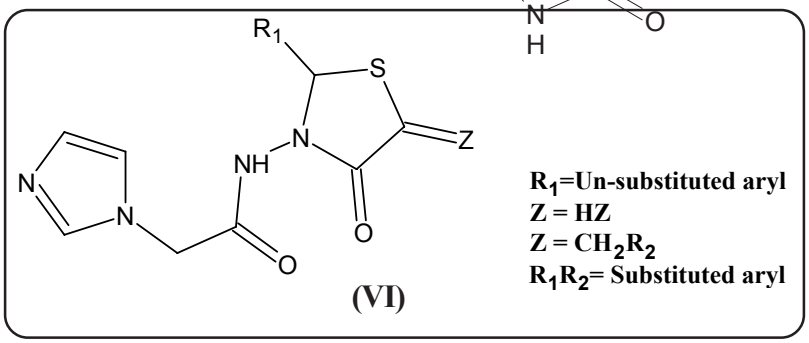
Akama Tsutoma et. al.[597] have synthesized thiazolidinones as a Telomeres inhibitors. S. Guniz Kucukguzel et. al.[598] have synthesized thiazolidinones as antimicrobial and anticancer agent. S. K. Srivastava et. al.[599] have prepared new thiazolidinones as antibacterial, antifungal, analgesic and diuretic agents.

Recently, Fujiwara Norio et. al.[600] have synthesized thiazolidinones as antiinflammatory agent. Pfahl Magnus et. al.[601] have reported thiazolidinones and tested their phosphatase inhibitory and anticancer activity. Jag Mohan et. al.[602]have prepared thiazolidinones (V) and reported their antimicrobial activity.



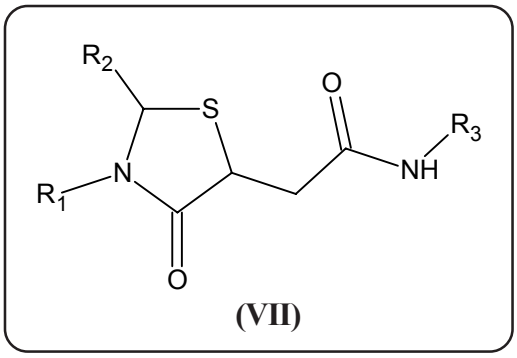
Govindarajan R. et. al.[603] have synthesized thiazolidinones as antitubercular, antifungal and antibacterial agent. Dinh T. H. et. al.[604] have prepared and reported antibacterial and antifungal activity of thiazolidinones. Takagi Masae and co-workers[605] have synthesized thiazolidinones and screened for their antiinflammatory activity. Ma Tonghui et. al.[606] have documented thiazolidinones as CFTR (cystic fibrosis transmembrane conductance regulator) inhibitor.

Hassan et. al.[607] have prepared 2-imino-4-thiazolidinones which have been found to possess antimicrobial activity. K. Mogilaiah and co-workers[608,609] isolated some 4-thiazolidinone derivatives and tested their antibacterial activity. G. S. Godaginamath et. al.[610] also prepared thiazolidinone derivatives as antimicrobial agent. R. S. Lodhi and co-workers[611] have been synthesized and studied antimicrobial, antiinflammatory and analgesic property of 4-thiazolidinone and arylidene derivatives (VI).



Recently, Dayam R. et. al.[612] have reported some novel thiazolidinone derivatives as novel class of HIV- integrase inhibitors. Sonawane N. D. et. al.[613] have synthesized some new thiaolidinone derivatives as *in vivo* pharmacology and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents. Shih M. H. et. al.[614] have described the syntheses and evaluation of antioxidant activity of sydnonyl substituted thiazolidinone

and thiazoline derivatives(VII). Reigada D. et. al.[615] have reported some novel thiazolidinone derivatives as release of ATP from retinal pigment epithelial cells involves both CFTR and vesicular transport.

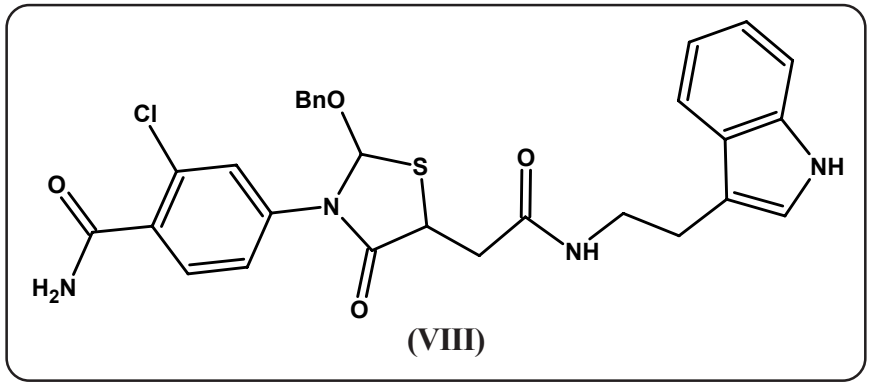


(VII)

Moreover, Rao A. et. al.[616] have described some novel thiazolidinone derivatives as 2-(2,6-dihalophenyl)-3-(pyrimidin-2-yl)-1,3-thiazolidin-4-ones as non-nucleoside HIV-1 reverse transcriptase inhibitors. Muanprasat C. et. al.[617] have prepared some new thiazolidinone derivatives as CFTR inhibitors.

Furthermore, Salinas D. B. et. al.[618] documented the thiazolidinone derivatives as CFTR inhibitor. Wang X. F. et. al.[619] have synthesized some novel thiazolidinone derivatives described as new cystic fibrosis transmembrane conductance regulator inhibitor on Cl-conductance in human sweat ducts. Ur F. et. al.[620] have constructed some new 6-methylimidazo[2,1-b]thiazole-5-carbohydrazide derivatives and their antimicrobial activities.

Recently, Maclean D. et. al.[621] have reported thiazolidinone library as agonists of the follicle stimulating hormone receptor (VIII). Thiagarajah J. R. et. al.[622] have synthesized a small molecule as CFTR inhibitor.



(VIII)

Thiagarajah J. R. et. al.[623] have been reported as intestinal ion and fluid secretion by a small-molecule CFTR inhibitor. Taddei A. et. al.[624] have been constructed some new thiazolidinone as CFTR inhibition.

These valid observations led us to explore thiazolidinones chemistry by synthesizing its derivatives bearing pyrazole moiety of medicinal value in order to achieve better therapeutic agents. It has been described in the following section.

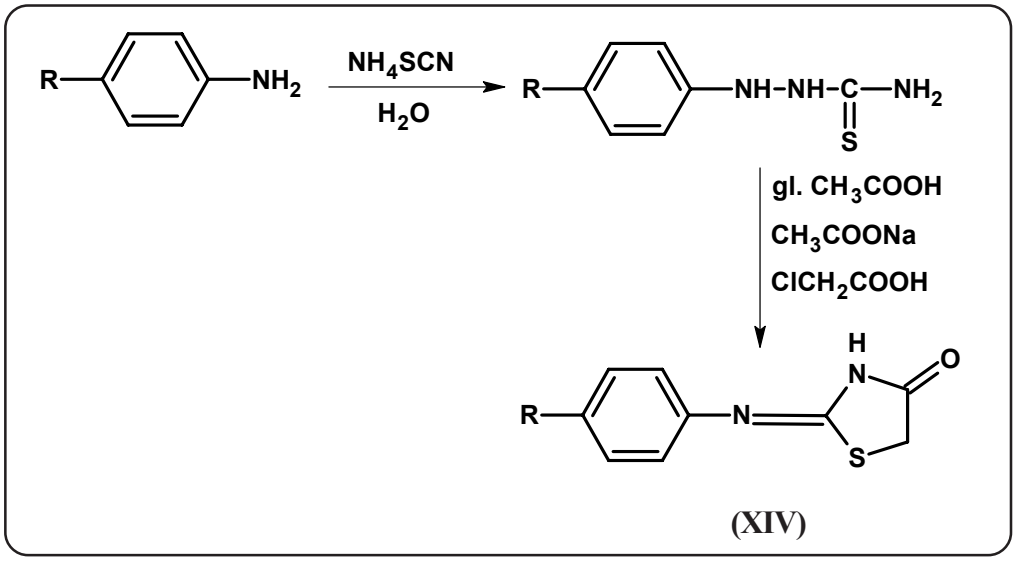
SECTION - I **SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-5(H)-4-THIAZOLIDINONES**

SECTION - II **SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL-METHINO)-4-THIAZOLIDINONE**

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-5(H)-4-THIAZOLIDINONES

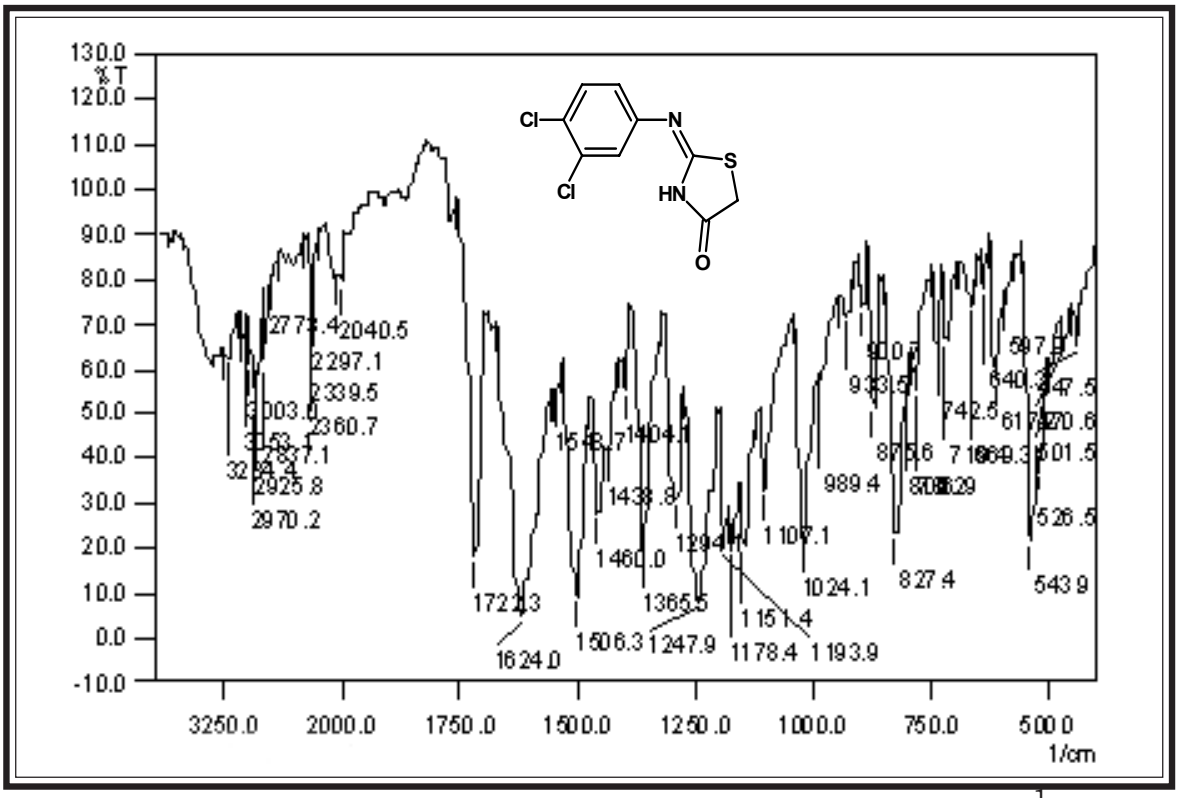
Looking to the interesting therapeutic activities of thiazolidinones, we have synthesised thiazolidinone of type- (XIV) by action of substituted aryl thiosemicarbazone with chloroacetic acid, sodium acetate in the presence of gl. acetic acid.



(XIV)

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy. The mass spectra of 2-(3,4Dicholorphenylimino)-5(H)-4-thiazolidinone give m/z = 261(recorded on Page No. 199). The fragmentation is also explained (Page No. 200).

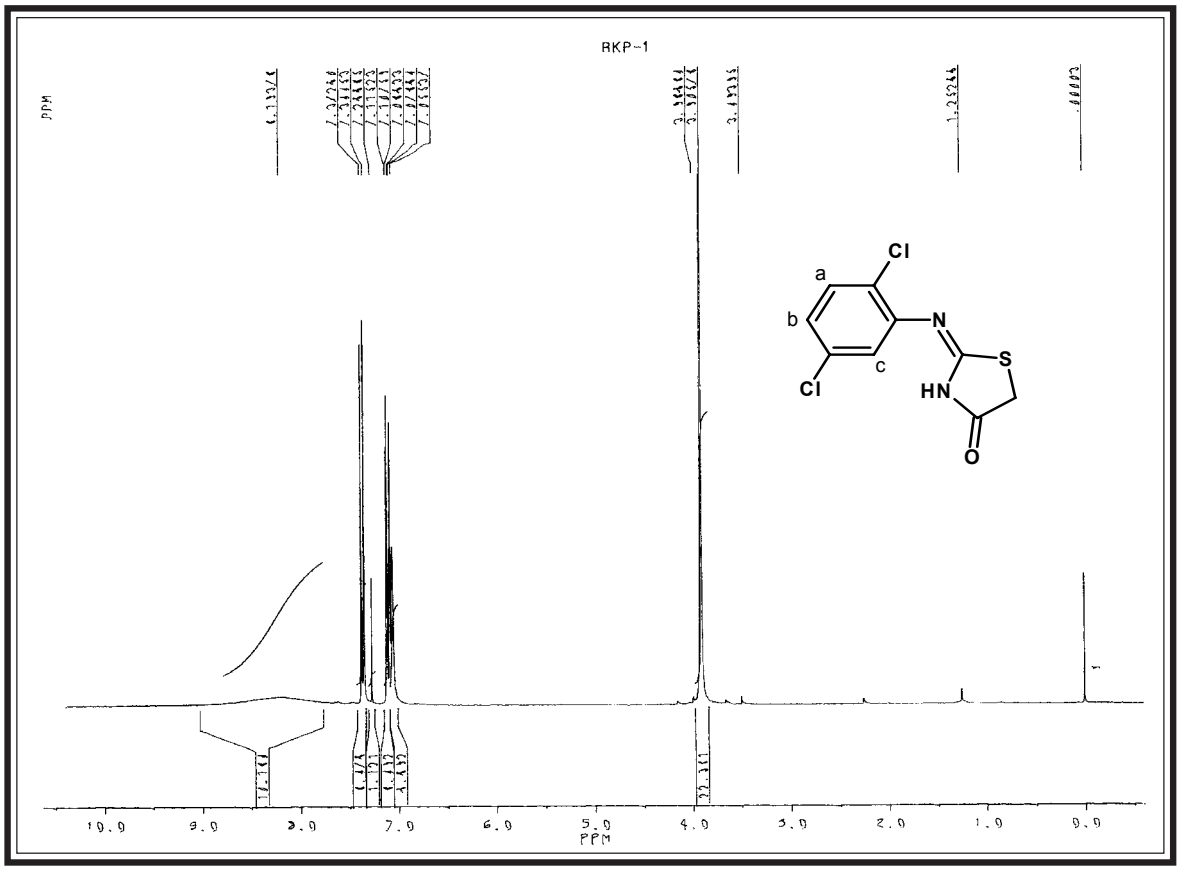
IR SPECTRAL STUDY OF 2-(3',4'-DICHLOROPHENYLIMINO)-5(H)-4-THIAZOLIDINONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

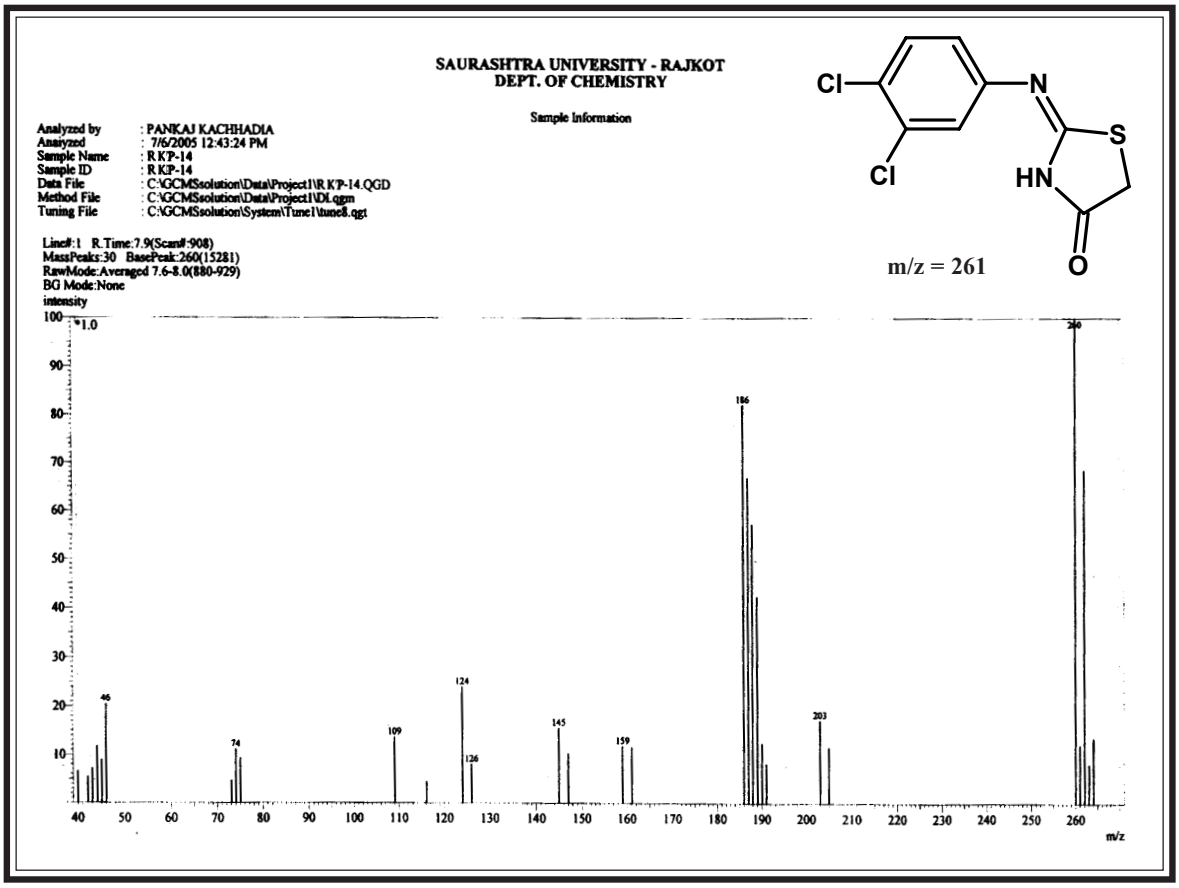
Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2933	2975–2950	426
$-CH_3$	C – H str. (sym.)	2835	2880–2860	"
	C – H i.p. (def.)	1450	1470–1435	"
	C – H o.o.p. (def.)	1361	1385–1350	"
Aromatic	C – H str.	3049	3130–3030	427
	C = C str.	1502	1585–1480	"
	C – H i.p. (def.)	1064	1125–1090	"
	C – H o.o.p. (def.)	833	835-810	"
Pyrazole	C = N str.	1606	1650–1580	428
moiety	C – N str.	1259	1350–1200	"
	C – F	752	760-710	"
Ether	C – O – C str. (asym).	1220	1275–1200	"
	C – O – C str. (sym).	1029	1075–1020	"
Chalcone	C = O str.	1660	1760–1655	429

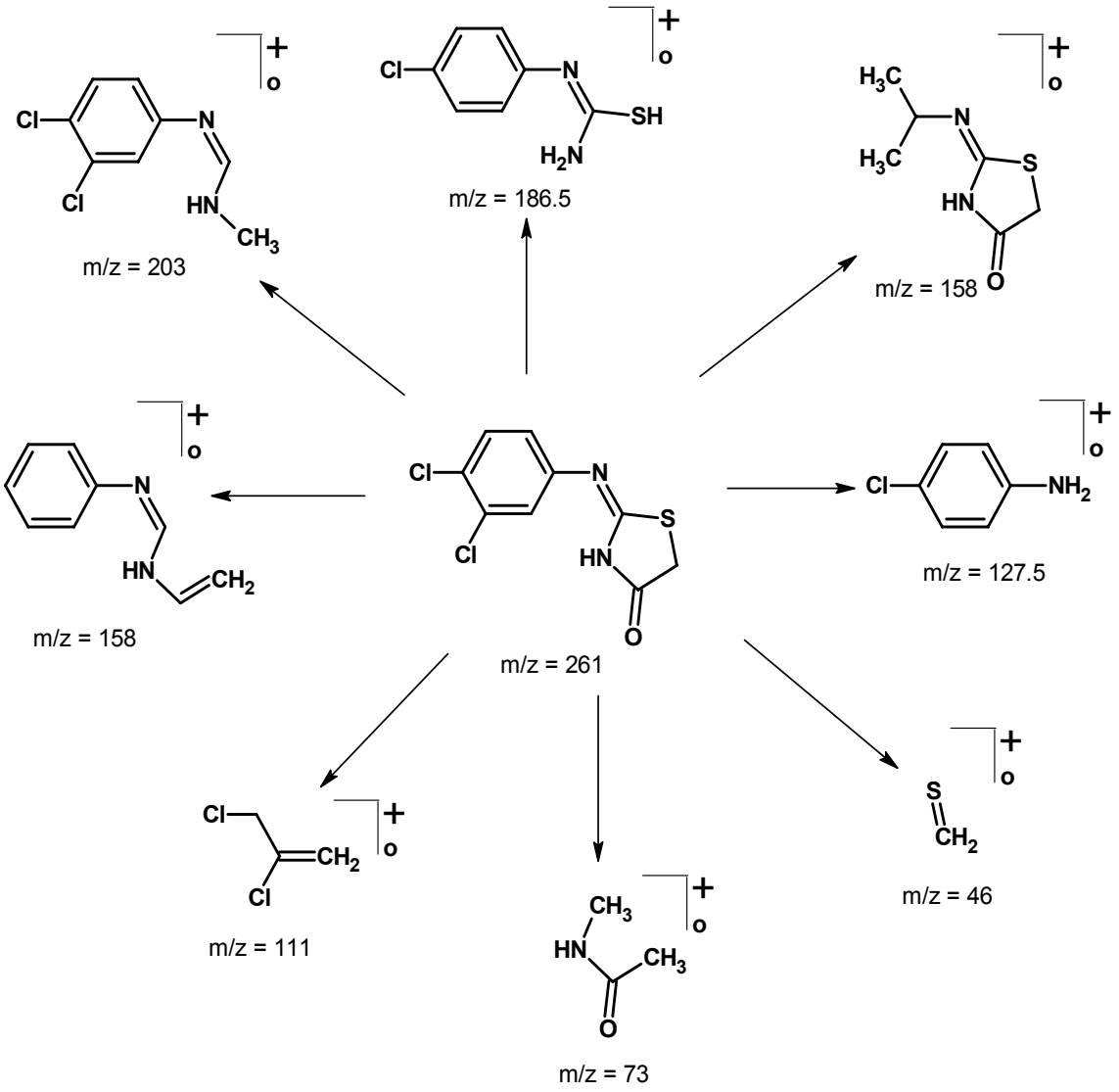
PMR SPECTRAL STUDY OF 2-(2',5'-DICHLOROPHENYLIMINO)-5(H)-4-THIAZOLIDINONE



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.98	2H	singlet	$-CH_2$	-
2.	7.05	1H	singlet	Ar-Hc	-
3.	7.07-7.11	1H	double doublet	Ar-Hb	Jba = 8.7
4.	7.34-7.37	1H	doublet	Ar-Ha	Jab = 8.42

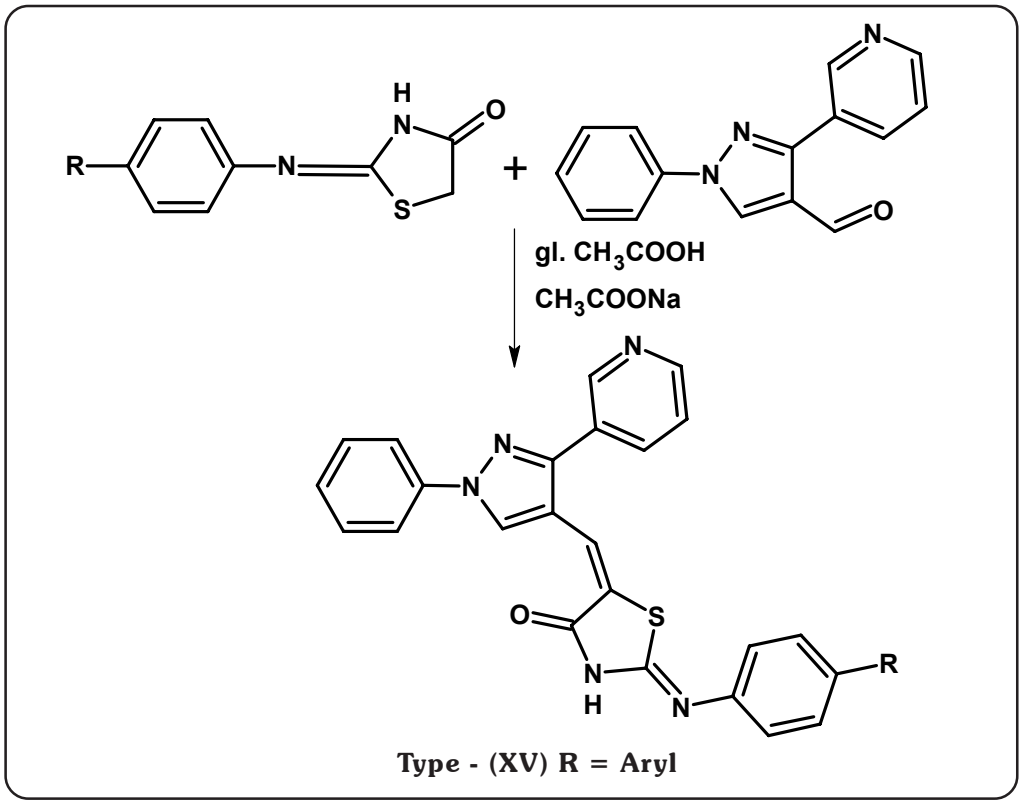

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY
Sample Information
Analyzed by : PANKAJ KACHHADIA
Analyzed : 7/6/2005 12:43:24 PM
Sample Name : R KP-14
Sample ID : R KP-14
Data File : C:\GCMSsolution\Data\Project1\R KP-14.QGD
Method File : C:\GCMSsolution\Data\Project1\DL.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune8.qgt
Line#:1 R.Time:7.9(Scan#:908)
MassPeaks:30 BasePeak:260(15281)
RawMode:Averaged 7.6-8.0(880-929)
BG Mode:None
intensity
Cl
Cl
N
S
HN
O
m/z = 261
m/z


m/z = 203
m/z = 186.5
m/z = 158
m/z = 158
m/z = 261
m/z = 127.5
m/z = 111
m/z = 73
m/z = 46

SECTION - II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL-METHINO)-4-THIAZOLIDINONES

With a view to getting better therapeutic agents and considering the association of various biological activities of thiazolidinone heterocycles, the preparation of arylidenes of Type (XIV) have been undertaken by the condensation of 1,NPhenyl-3-(â-pyridyl)-4-formyl pyrazole with different 2-Arylimino-5(H)-4-thiazolidinones.

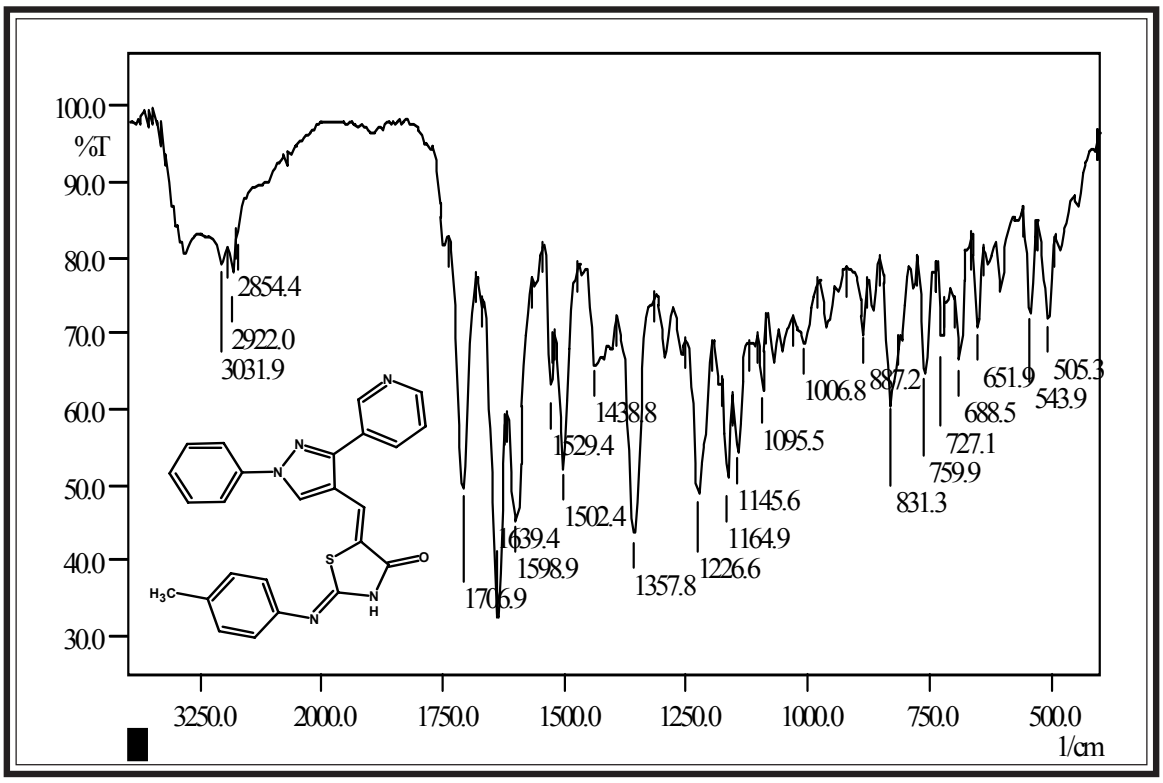


Type - (XV) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. The mass spectra of 2-p-Anisylimino-5-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl-methino)-4-thiazolidinone give m/z =450(recorded on Page No. 204). The fragmentation is also explained (Page No. 205).

The products have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards *Aspergillus niger* at a concentration of 40 mg/ml. The biological activities of synthesised compounds were compared with standard drugs.

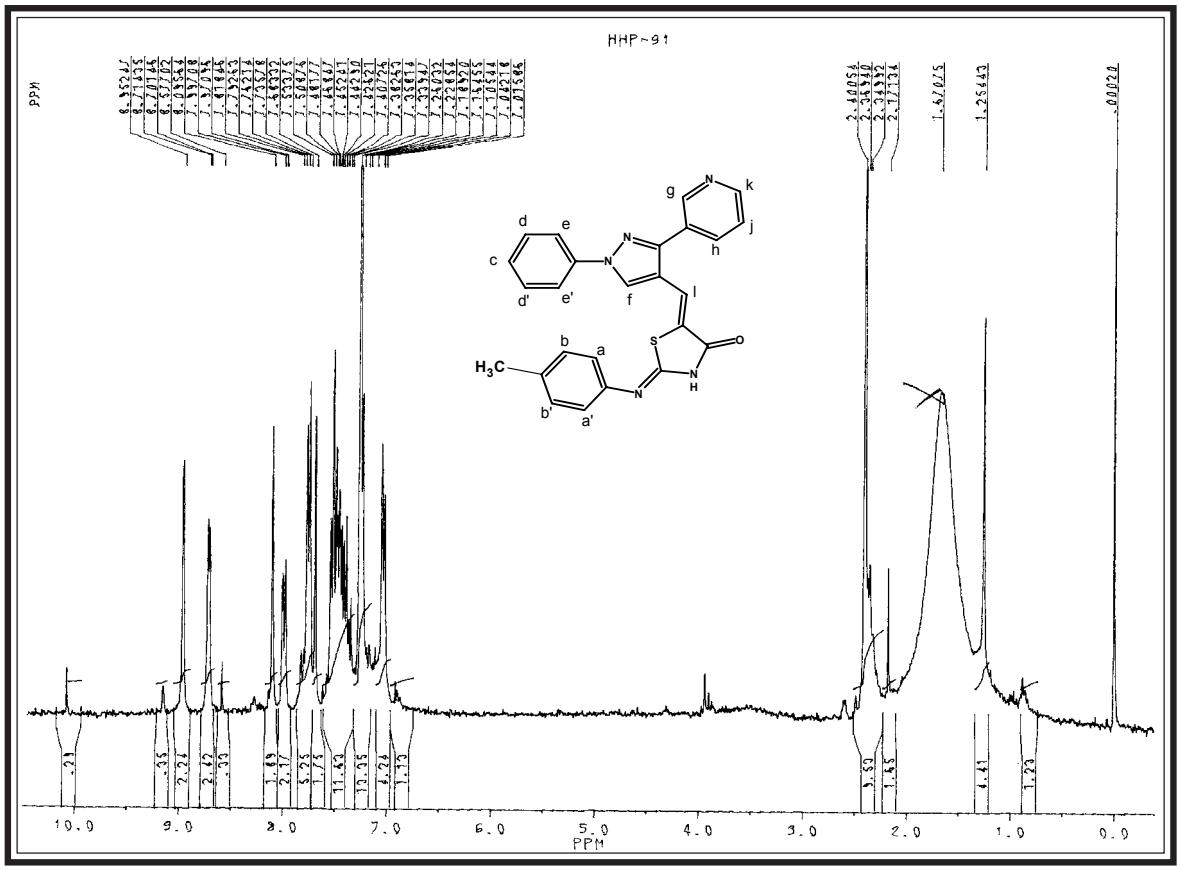
IR SPECTRAL STUDIES OF 2-(p-TOLYLIMINO)-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL-METHINO)-4-THIAZOLIDINONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2922	2975-2925	95
-CH_3	C-H str. (sym.)	2854	2880-2860	,,
	C-H i.p.(def.)	1438	1470-1435	,,
	C-H o.o.p. (def)	1357	1395-1370	,,
Aromatic	C-H str.	3031	3090-3030	96
	C=C str.	1502	1540-1480	,,
	C-H i.p.(def.)	1095	1125-1090	,,
	C-H o.o.p.(def)	831	835-810	,,
Pyrazole	C=N str.	1598	1600-1650	72
moiety	C-N str.	1226	1220-1020	,,
Thiazolidinone	C=O str.	1706	1760-1655	95
ring	C-S-C str.	688	700-600	,,
	C-N str.	1164	1220-1020	,,
	C=N str.	1639	1640-1590	,,

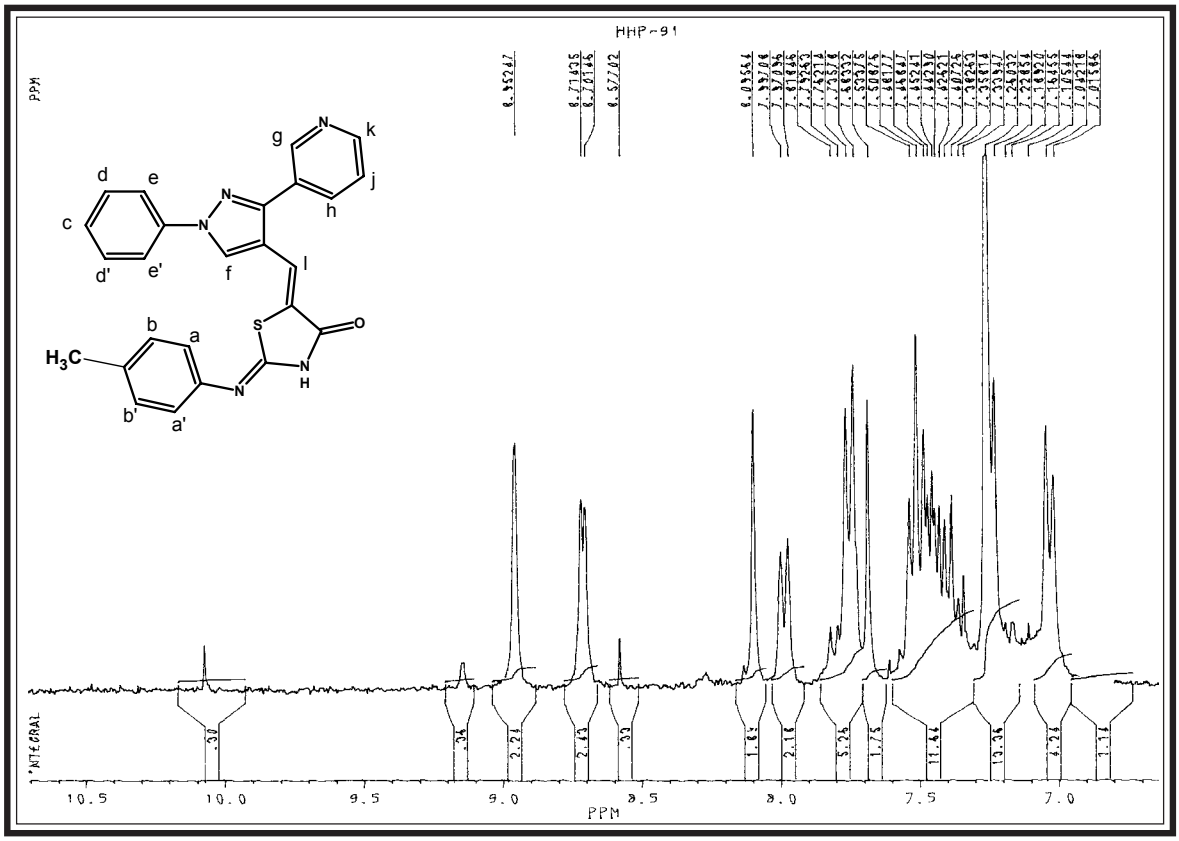
PMR SPECTRAL STUDY OF 2-(p-TOLYLIMINO)-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL -4'-YL-METHINO)-4-THIAZOLIDINONE

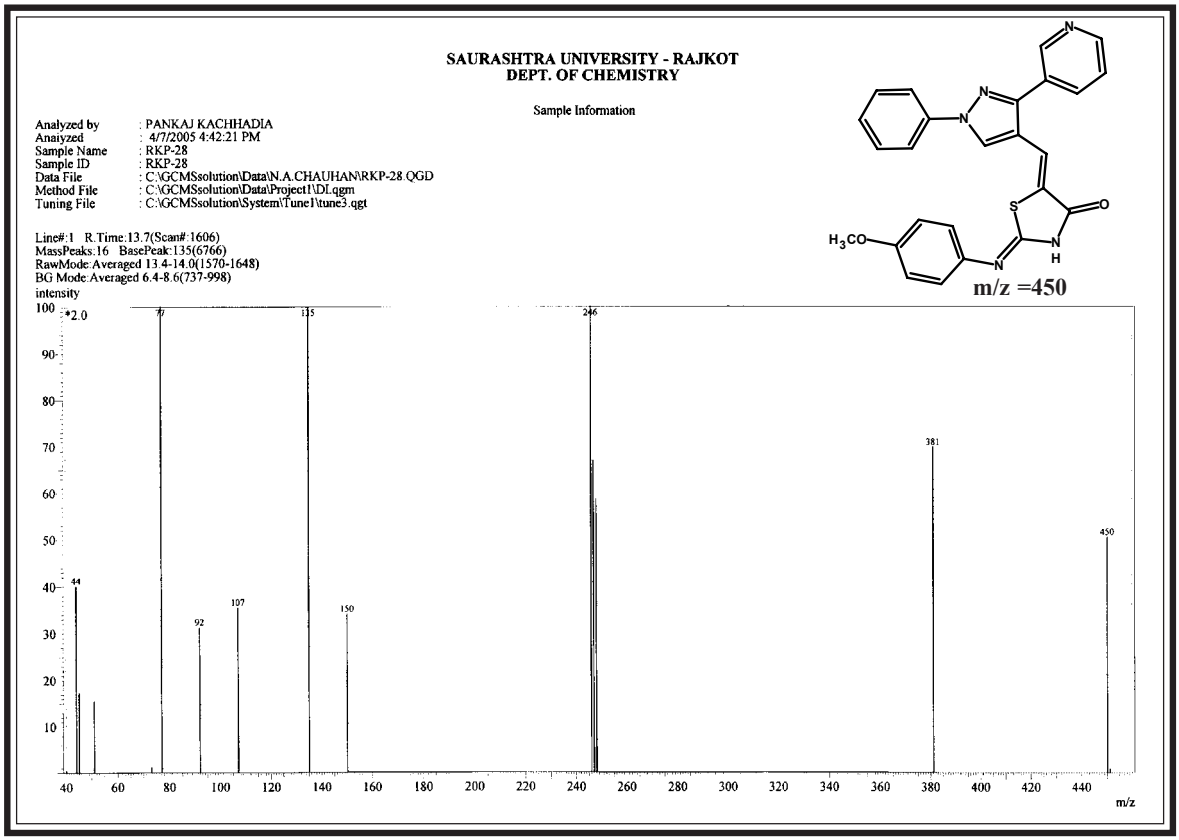


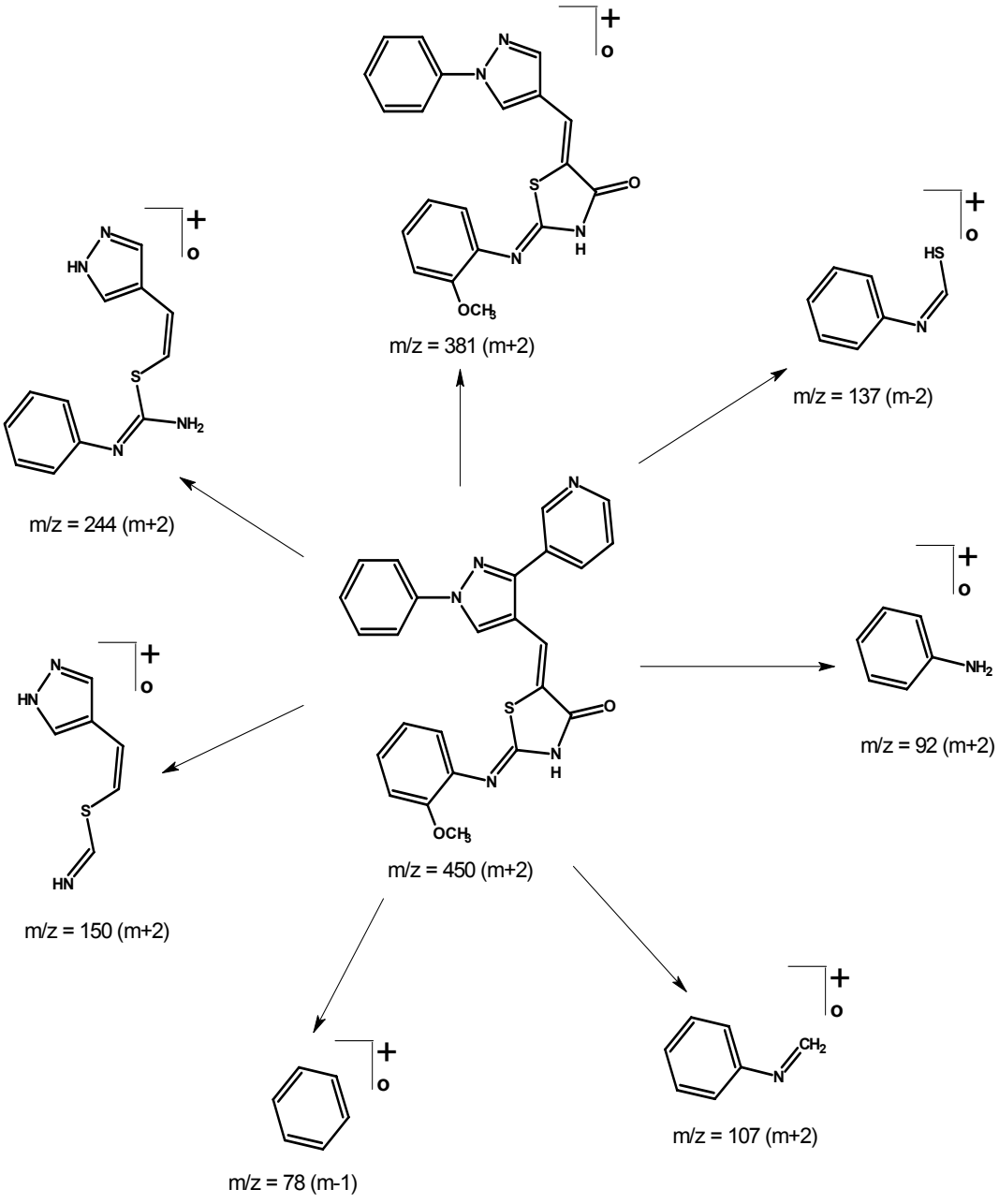
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1	2.4	3H	singlet	Ar-CH_3	-
2	7.01-7.04	2H	doublet	Ar-Ha,a'	Jaa'=7.9
3	7.22-7.26	2H	multiplet	Ar-Hc,j	-
4	7.35-7.44	1H	multiplet	Ar-Hh	-
5	7.48-7.53	4H	multiplet	Ar-Hb,b'	-
				Ar-Hd,d'	-
6	7.68	1H	singlet	-NH	-
7	7.76-7.79	2H	doublet	Ar-He,e'	Jee'=8.1
8	7.97-8.0	1H	doublet	Ar-Hk	Jkj=7.8
9	8.09	1H	singlet	Ar-Hl	-
10	8.70-8.71	1H	doublet	Ar-Hg	-
11	8.95	1H	singlet	Ar-Hf	-

EXPANDED AROMATIC REGION






m/z = 381 (m+2)
m/z = 137 (m-2)
m/z = 244 (m+2)
m/z = 92 (m+2)
m/z = 450 (m+2)
m/z = 150 (m+2)
m/z = 107 (m+2)
m/z = 78 (m-1)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL-METHINO)-4-THIAZOLIDINONES

[A] Synthesis of 3-Acetyl pyridine phenyl hydrazone

See, Part-I, Section-I (A).

[B] Synthesis of 1,N-Phenyl-3-â-pyridyl-4-fromyl pyrazole

See, Part-I, Section-I (B).

[C] Synthesis of 2-(p-Tolylimino)-5-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl-methino)-4-thiazolidinone

To a well stirred solution of 1N-Phenyl-3-â-pyridyl-4-fromyl-pyrazole (2.65gm, 0.01M) and p-Tolylimino-5H-4-thiazolidinone and fused sodium acetate (1.64 g, 0.02M) was refluxed in glacial acetic acid on oil bath for 12 hrs, cooled and poured into ice cold water. Crude was isolated and treated with sodium bisulphide. The solid thus obtained was filtered, washed, dried and crystallised from DMF. Yield,62%, m.p.222^{o}C. ($C_{25}H_{19}N_5OS$; Found : C,75.33%; H, 4.77%; N, 15.99%; Requires : C, 75.36%; H, 4.81%; N, 16.01%).

Similarly, other substituted chalcones have prepared. The physical data are recorded in Table No. 13.

[D] Antimicrobial activity of 2-Aryl-5-(1',N-phenyl-3'-â-pyridyl-pyrazol-4'-yl-methino)-4-thiazolidinones

Antimicrobial testing was carried out as described in Part-I, Section-II (C). The zone of inhibition of the test solution are recorded in Graphical Chart No. 13.

Antitubercular screening of the compounds of type(XV) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-II (C) and the percentage of inhibition data of the compounds are recorded in Table No. 13a.

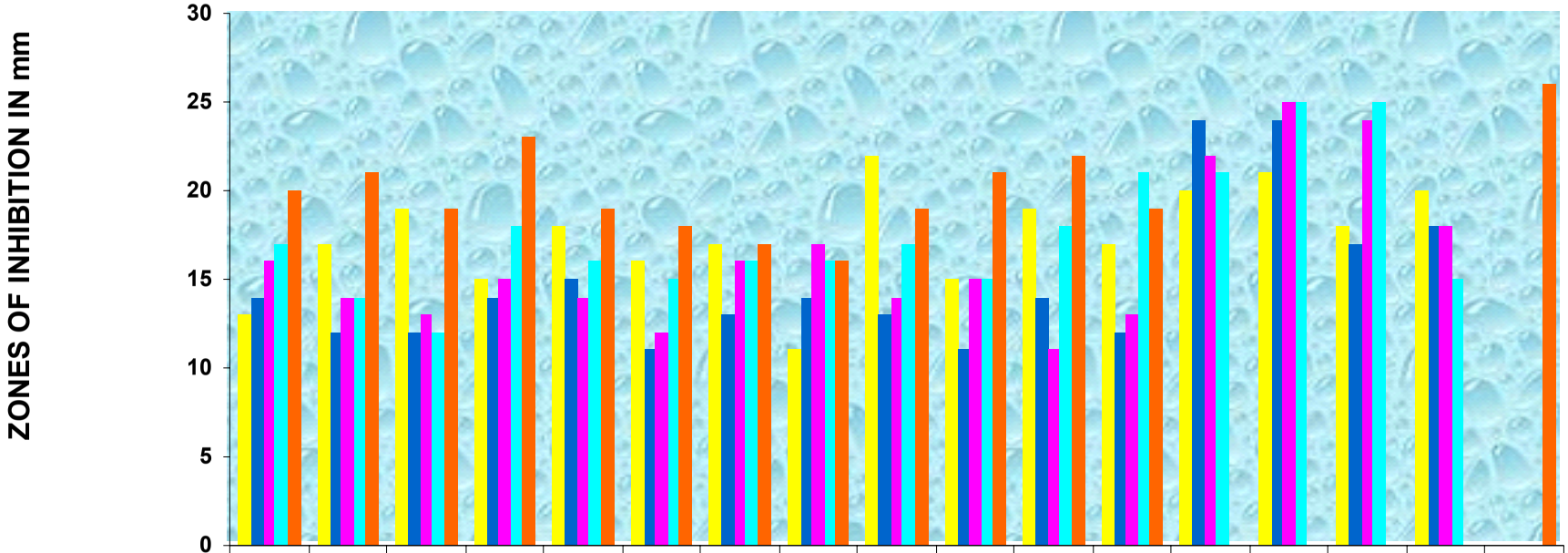
TABLE NO. 13 : PHYSICAL CONSTANTS OF 2-ARYLIMINO-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL-METHINO)-4-THIAZOLIDINONES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. ^{o}C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
13a	2-CH_3-C_6H_4-	$C_{25}H_{19}N_5OS$	437	194	0.42	60	16.01	15.97
13b	4-CH_3-C_6H_4-	$C_{25}H_{19}N_5OS$	437	222	0.48	62	16.01	15.99
13c	2-OCH_3-C_6H_4-	$C_{25}H_{19}N_5O_2S$	453	207	0.37	57	15.44	15.42
13d	4-OCH_3-C_6H_4-	$C_{25}H_{19}N_5O_2S$	453	186	0.52	65	15.44	15.40
13e	3-Cl-C_6H_4-	$C_{24}H_{16}ClN_5OS$	457.5	178	0.47	49	15.29	15.27
13f	4-Cl-C_6H_4-	$C_{24}H_{16}ClN_5OS$	457.5	167	0.55	56	15.29	15.28
13g	4-F-C_6H_4-	$C_{24}H_{16}FN_5OS$	441	201	0.44	59	15.86	15.84
13h	4-Br-C_6H_4-	$C_{24}H_{16}BrN_5OS$	502	236	0.39	49	13.94	13.91
13i	4-NO_2-C_6H_4-	$C_{24}H_{16}ClN_6O_2S$	468	190	0.57	57	17.94	17.92
13j	3,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{16}Cl_2N_5OS$	492	229	0.60	63	14.22	14.20
13k	2,5-$(Cl)_2$-C_6H_3-	$C_{24}H_{16}Cl_2N_5OS$	492	163	0.52	60	14.22	14.18
13l	2,4-$(CH_3)_2$-C_6H_3	$C_{26}H_{21}N_5OS$	451	172	0.49	54	15.51	15.49

*TLC Solvent System : Acetone : Benzene

3 : 7

GRAPHICAL CHART NO. 13 : ANTIMICROBIAL ACTIVITY OF 2-ARYLIMINO-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL-METHINO)-4-THIAZOLIDINONES

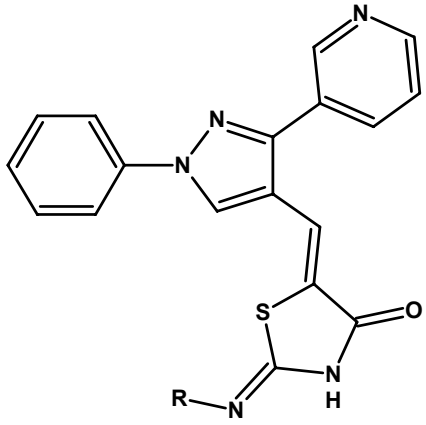


	13a	13b	13c	13d	13e	13f	13g	13h	13i	13j	13k	13l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. cocous	13	17	19	15	18	16	17	11	22	15	19	17	20	21	18	20	0
B. substilus	14	12	12	14	15	11	13	14	13	11	14	12	24	24	17	18	0
E.coli	16	14	13	15	14	12	16	17	14	15	11	13	22	25	24	18	0
P. vulgaris	17	14	12	18	16	15	16	16	17	15	18	21	21	25	25	15	0
A. niger	20	21	19	23	19	18	17	16	19	21	22	19	0	0	0	0	26

BIOLOGICAL EVALUATION OF 2-ARYLIMINO-5-(1',N-PHENYL-3'-â-PYRIDYL-PYRAZOL-4'-YL-METHINO)-4-THIAZOLIDINONES

Antibacterial Activity zone of inhibition in mm				Antifungal Activity zone of inhibition in mm
B. cocous	*B. subtillus*	*E. coli*	*P. vulgaris*	*A. niger*
1	2	3	4	5
13f(19)		13h(17)	13l(21)	13a(19)
13a(18)			13d(18)	13h(19)
13e(18)			13k(18)	13d(23)
			13a(17)	
			13i(17)	
			13e(16)	
			13g(16)	
			13h(16)	
Comparable activity with standard drugs				
Benzoylpenicillin(18)	Amoxycillin(18)	Benzoylpenicillin(25)	Benzoylpenicillin(25)	Greseofulvin(26)
Erythromycin(20)	Benzoylpenicillin(24)	Ciprofloxacin(24)	Ciprofloxacin(25)	

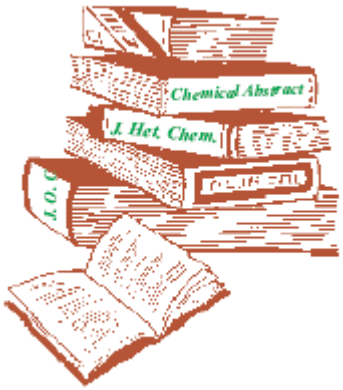
TABLE NO. 13a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC mg/ml*	*% Inhib*	*Activity*	*Comment*
RKP-55	295723	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	21	-	MIC Rifampin =
RKP-56	295724	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	0.25 mg/ml
RKP-57	295725	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	17	-	@ 98% Inhibition
RKP-58	295726	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	16	-	"
RKP-59	295727	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-60	295728	2-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	11	-	"
RKP-61	295729	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
RKP-62	295730	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	89	-	"
RKP-63	295731	3,4(Cl)$_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	32	-	"
RKP-64	295732	2,4-$(CH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	46	-	"



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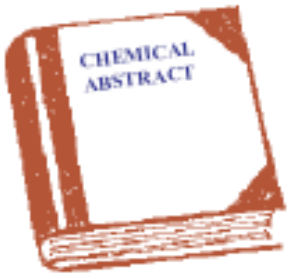

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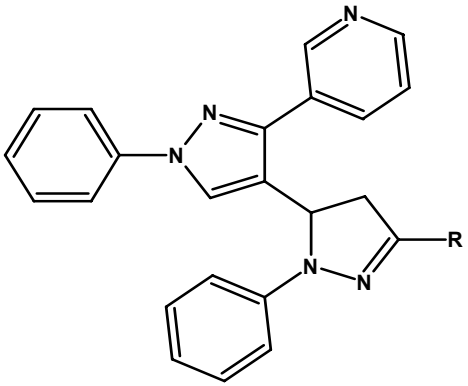

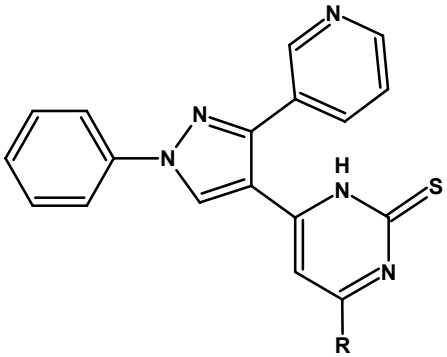

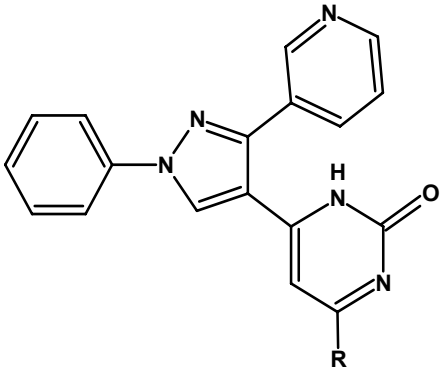

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4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
2-OH-C_6H_4-	2-OH-C_6H_4-	2-OH-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-	4-OH-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-F-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Br-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
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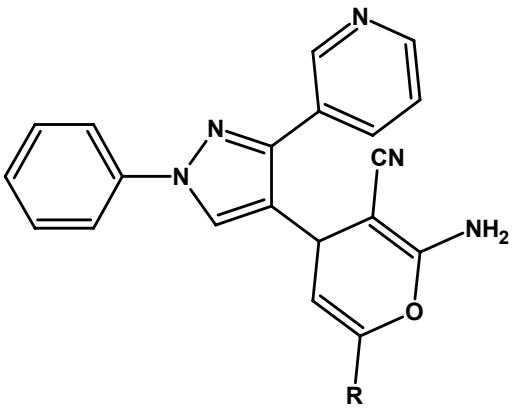

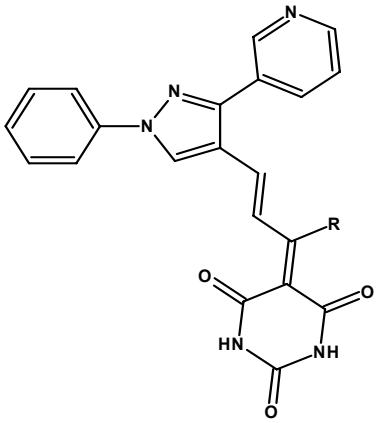

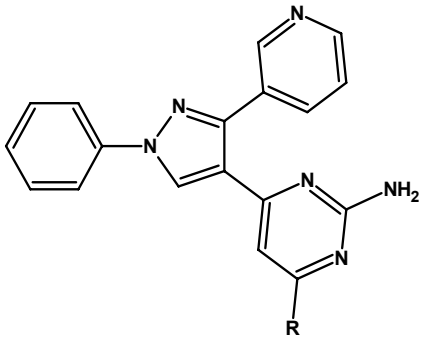

R	R	R
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4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
2-OH-C_6H_4-	2-OH-C_6H_4-	2-OH-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-	4-OH-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-F-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Br-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
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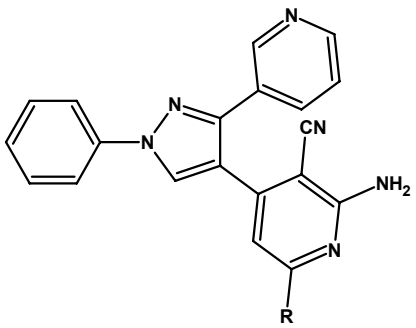

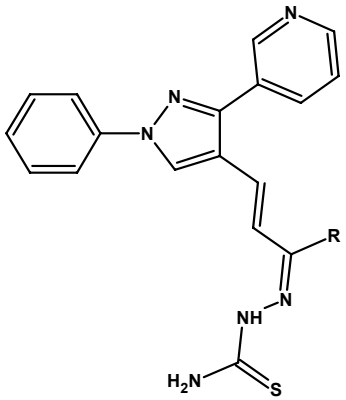

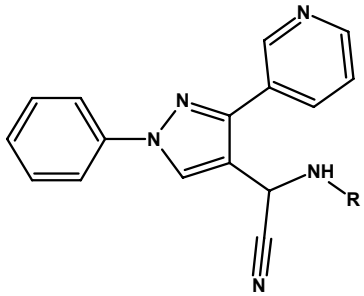

R	R	R
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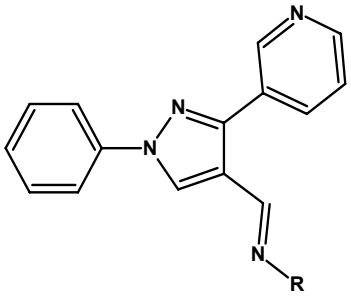
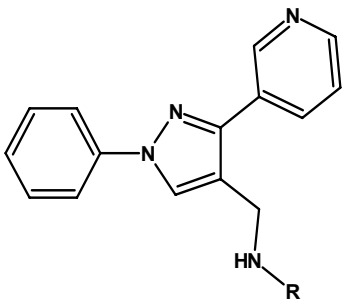
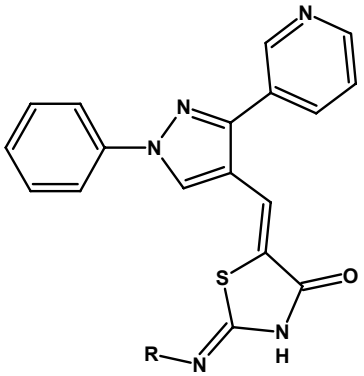
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-CH_3-C_6H_4-
2-OH-C_6H_4-	2-OH-C_6H_4-	2-OCH_3-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-	3-OCH_3-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-OCH_3-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	3-Cl-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Cl-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-	2-F-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	4-F-C_6H_4-
4-NH_2-C_6H_4-	4-NH_2-C_6H_4-	4-Br-C_6H_4-
		4-NO_2-C_6H_4-
		2,4-$(CH_3)_2$-C_6H_3







R	R	R
2-CH_3-C_6H_4-	2-CH_3-C_6H_4-	2-CH_3-C_6H_4-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
2-OCH_3-C_6H_4-	2-OCH_3-C_6H_4-	2-OCH_3-C_6H_4-
3-OCH_3-C_6H_4-	3-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	3-Cl-C_6H_4-
3-Cl-C_6H_4-	3-Cl-C_6H_4-	4-Cl-C_6H_4-
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2-F-C_6H_4-	2-F-C_6H_4-	4-Br-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-NO_2-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-	3,4-$(Cl)_2$-C_6H_3-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	2,5-$(Cl)_2$-C_6H_3-
2,4-$(CH_3)_2$-C_6H_3	2,4-$(CH_3)_2$-C_6H_3	2,4-$(CH_3)_2$-C_6H_3-